Synthesis of a photoswitchable acceptor molecule.

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SYNTHESIS OF A PHOTOSWITCHABLE ACCEPTOR MOLECULE

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I would finally like to mention Swansea University Chemistry Department. I spent eight years of my life there, thoroughly enjoyed myself and learnt a great deal. If all that is to be left of it are memories, at least they'll be good ones.

Summary

The aim of this project was to design a photochromic molecule that could be linked to a derivative of the fluorophore *N*-methylacridone, and would have properties such that one form of the molecule would have no effect on the fluorescence and the other form of the molecule would quench the fluorescence through resonance energy transfer. The ultimate result would be a switchable fluorescent molecule.

The first chapter contains the background of the project including the selection of an appropriate photochromic molecule from the literature and the design of and planned synthetic routes to the target molecule, a modified linkable version of the molecule found in the literature.

The second chapter details the successful development of a method for the regioselective 5-substitution of 3-methylthiophene *via* lithiation with lithium 2,2,6,6-tetramethylpiperidide. It also details the use of that method in the synthesis of several derivatives of 3-methylthiophene, some of which were essential for the later stages of the project, others of which had been previously synthesised unsatisfactorily and others of which were novel compounds.

The third chapter details the synthesis of the photochromic parent molecule 1,2-bis(3,5-dimethyl-2-thienyl)perfluorocyclopentene and the evaluation of the closed form of that molecule as an energy transfer acceptor for *N*-methylacridone. The closed form was found theoretically to be a viable acceptor at the donor-acceptor distance in question. It also details the first attempted synthesis of the linkable target molecule *via* the synthesis of 3-(4-methyl-2-thienyl)-1-propylamine and subsequent synthesis of several protected derivatives. The attempted synthesis of the target molecule using those protected derivatives was ultimately unsuccessful, however several novel compounds were synthesised in the attempt.

The fourth chapter details the successful synthesis of the linkable photochromic target molecule *via* several novel photochromic compounds, the photochromism of which was demonstrated. The closed form of the linkable target molecule was evaluated as an energy transfer acceptor for *N*-methylacridone and was found theoretically to be viable.

Contents

Chapter One:

Introduction

1.1. *N*-Methylacridone.

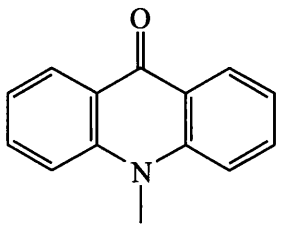

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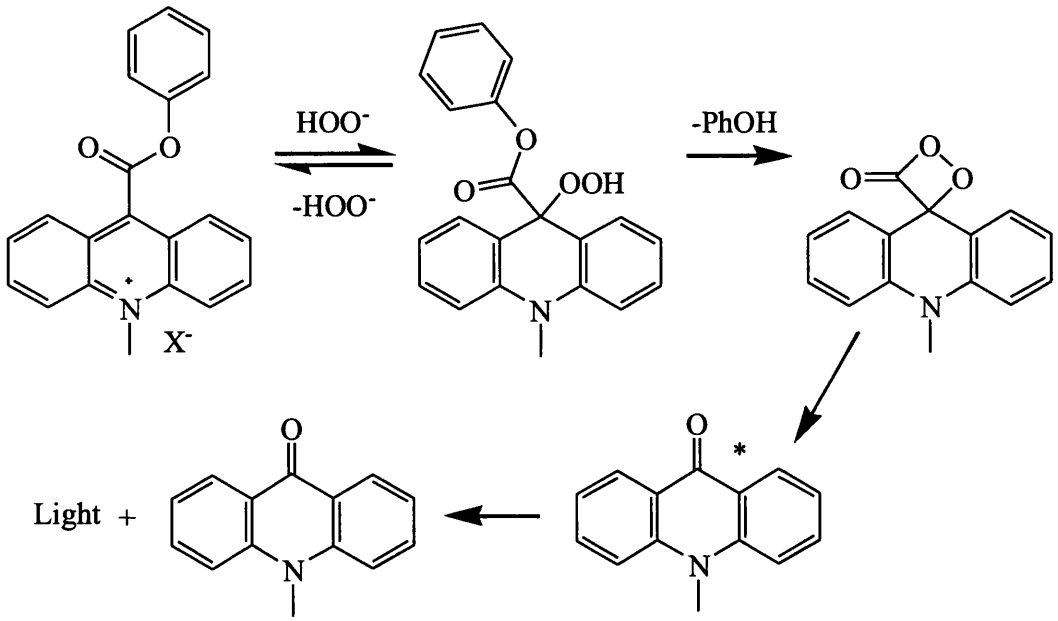
Figure 1.1: *N*-Methylacridone

N-Methylacridone (**1**, **Figure 1.1**.) is a fluorescent molecule, the low toxicity, high fluorescence quantum yield[1] and consequent high detection sensitivity of which makes it a useful species for applications in chemiluminescence immunoassay, in the place of more hazardous radioisotopes.[2]

The Centre for Clean Chemistry in Swansea has an extensive history of work in the area of synthesis of novel chemiluminescent acridinium esters that undergo a chemiluminescent reaction to produce excited **1**.[3] An example of this chemiluminescent reaction is shown in **Scheme 1.1.**



Scheme 1.1: A representative example of the chemiluminescent reaction of acridinium esters.

1.2. Project outline.

The idea behind the project that is reported in this thesis concerned a novel extension to the work in the area of acridinium esters. It was known that the phenomenon of resonance energy transfer (RET – Section 1.3), the non-radiative quenching of fluorescence by an acceptor molecule, had several applications such as protein assembly studies and microscopy.[4] As **1** has in the past proved to be an ideal fluorophore for practical applications,[3] it was thought that it would be interesting to include it in a novel RET-capable system. The phenomenon of organic photochromism, the light-induced reversible conversion of a molecule between two forms with different UV absorptions and usually different colours (Section 1.4.) was considered, and the idea for a novel RET-capable system was formulated.

It was thought that if a photochromic molecule could be found that absorbed light at the reported emission maximum of **1** ($\lambda = 426$ nm, MeOH[1]) in one form but not in the other and that molecule could be somehow chemically linked to the fluorophore then the resulting product would be a "switchable" fluorescent molecule, which is represented in **Figure 1.2.**

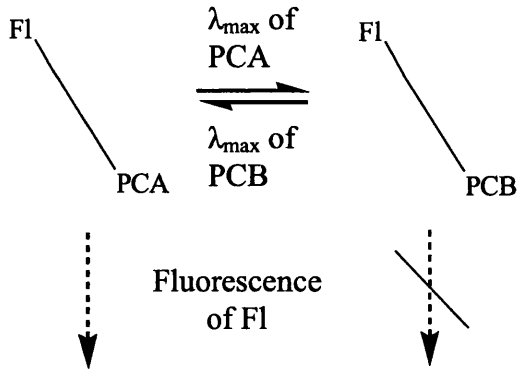


Figure 1.2: Theoretical behaviour of the proposed switchable donor-acceptor molecule: A fluorophore (Fl) is linked to one form of a photochromic molecule (the A-form; PCA) which does not quench the fluorescence of Fl. When PCA is photochemically switched to its second form (The B-form; PCB) the fluorescence of Fl is quenched.

This molecule would, in theory, have two forms. The first form would have the fluorophore (Fl) linked to the colourless form of a photochromic molecule (PCA) that did not quench its fluorescence; in this form the fluorescence of the fluorophore would be observed as normal. In the second form, the photochromic molecule would be converted to its coloured second form (PCB) which would quench the fluorescence of the

fluorophore; in this case excitation of the fluorophore would produce no fluorescence but would convert the photochromic molecule back to its original form, thus bleaching the colour. This was thought to have a variety of potential applications in the fields of bioanalysis, security marking, etc.

The aim of this project can therefore be summarised thus: to find in the literature or design a photochromic molecule that would quench the fluorescence of **1** in one form but not in the other, and to modify that photochromic molecule in such a way that it could conceivably be linked to a similarly linkable fluorophore but would not have its spectroscopic characteristics changed in the process.

In order to identify a photochromic molecule that would be a viable linker for the fluorophore in question it was necessary to identify the criteria by which that viability could be determined. In order to find these criteria it was necessary to investigate the theoretical background of RET.

1.3. Resonance energy transfer (RET).

1.3.1. Energy transfer.[4]

A simple representation of the transfer of energy from an excited fluorophore *donor* D* to an *acceptor* molecule A is shown in **Figure 1.3.**

$$D^* + A \rightarrow D + A^*$$

Figure 1.3: Energy transfer from an excited donor (D*) to an acceptor (A).

The phenomenon involves the transfer of electronic excitation energy from D* to A resulting in the relaxation of D* to its ground state D and the resulting excitation of A to its excited state A*, which can then emit the energy *via* fluorescence or other processes. The fluorescence of D* is said to have been be *quenched* by A.

Energy can be transferred radiatively, involving the simple emission of a photon from the donor which is then absorbed by the acceptor, or non-radiatively, *via* resonance energy transfer.

1.3.2. *Resonance energy transfer.*[4]

If two molecules have the appropriate properties energy can be transferred between them non-radiatively through long-range dipole-dipole interactions. The process is often referred to as Fluorescence Resonance Energy Transfer (FRET), but this is incorrect as no fluorescence is involved in the transfer of energy. The efficiency of energy transfer depends on the orientations of the dipoles of donor and acceptor relative to each other, the fluorescence quantum yield of the donor, the distance between the two molecules and the degree of overlap between the donor emission spectrum and the acceptor absorption spectrum. Theodor Förster derived the quantitative treatment of RET, which can be outlined starting with the rate of energy transfer (k_T), which is given in **Equation 1.1.**

$$k_T = 1/\tau_D (R_0/r)^6 \qquad \textbf{[Equation 1.1]}$$

The decay time of the donor in the absence of the acceptor is represented by τ_D, R_0 is the *Förster distance* and r is the distance between the donor and acceptor. The decay rate of the donor in the absence of the acceptor is represented by $1/\tau_D$, and it can be seen from the equation that if the separation between the donor and acceptor molecules (r) is equal to the Förster distance (R_0), then the rate of energy transfer (k_T) is simply equal to the decay rate of the donor in the absence of the acceptor ($1/\tau_D$). Therefore, when $r = R_0$ the efficiency of energy transfer is 50 %. It follows that the Förster distance can be defined as the separation at which the donor emission would be reduced to half its intensity in the absence of an acceptor, and as the separation at which half the donor molecules decay by energy transfer and half the donor molecules decay by normal processes. Also apparent from this equation is the large dependence of the rate of energy transfer on the separation of the donor and acceptor, as k_T is proportional to r^6.

The value of R_0 can be calculated from the measured spectroscopic properties of the donor and acceptor molecules as shown in **Equation 1.2.**

$$R_0 = 0.211[\kappa^2 n^{-4} \Phi_D J(\lambda)]^{1/6} \qquad \textbf{[Equation 1.2]}$$

This equation considers all the variables that are important to the efficiency of energy transfer. Φ_D is the quantum yield of emission of the donor, n is the refractive index of the medium in which energy transfer is taking place, κ^2 is the dipole orientation factor which

is usually taken to be 2/3 and J(λ) is the *spectral overlap integral*, which is a quantitative expression of the degree of overlap between the emission spectrum of the donor and the absorption spectrum of the acceptor. A representation of the spectral overlap integral is shown in **Figure 1.4**.

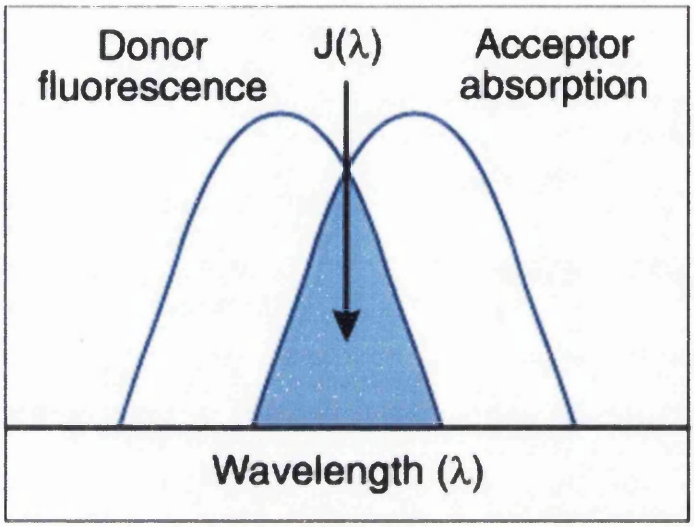


Figure 1.4: The spectral overlap integral J(λ).

The equation for the calculation of the spectral overlap integral is shown in **Equation 1.3.**

$$J(\lambda) = \int F_D(\lambda).\varepsilon_A(\lambda).\lambda^4 d\lambda \qquad \textbf{[Equation 1.3]}$$

$\int F_D(\lambda)$ is the integrated emission spectrum of the donor, normalised to unity, $\varepsilon_A(\lambda)$ is the integrated absorption spectrum of the acceptor with the wavelength plotted against the extinction coefficient ($dm^3mol^{-1}cm^{-1}$) and λ is the wavelength (nm). J(λ), therefore, has units of $dm^3mol^{-1}cm^{-1}nm^4$, and if this value of J(λ) is then used to calculate R_0 using **Equation 1.2** then the resulting value of R_0 will be in Angstroms (Å).

The usefulness of using the observed spectroscopic data of a donor acceptor pair to calculate J(λ) and R_0 for that pair lies in the indications that are given for the viability of the donor-acceptor pair. Common values of R_0 range between 20-60 Å and RET can be assumed to occur if the donor and acceptor separation is below R_0.[4a]

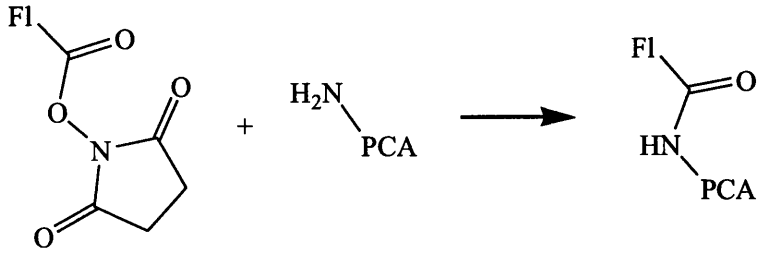
1.3.3. *Application of RET theory.*

This theory provided the starting point for the project. From the **Equations 1.1** to **1.3** it can be seen that the property of the donor that has bearing on the likelihood of RET taking place is the fluorescence quantum yield (Φ_D). The reported value for **1** is 0.89,[1] which is an extremely high value for this type of process and is encouraging. It can also be seen that the absorption spectrum of the acceptor, $\varepsilon_A(\lambda)$ is very important for efficient RET to occur, as is the separation of the donor and acceptor.

From this it can be concluded that a viable photochromic acceptor for **1** would have a λ_{max} of, or very close to, 426 nm in MeOH. This was therefore the criterion used in the search for a viable RET acceptor: A photochromic molecule that absorbed at 426 nm in one of its forms would be an applicable acceptor.

The dependence of RET efficiency on the donor-acceptor separation (r) was also considered important. As mentioned previously RET can be assumed to occur if the donor and acceptor separation is below R_0, and typical values of R_0 range between 20-60 Å. A plan to link **1** to a photochromic acceptor molecule would have to take this into account.

In order for linking to take place, the donor and acceptor molecules would each have to be modified so that they both possessed linker groups, for example the acceptor could contain an amino group and the donor could contain an *N*-hydroxysuccinimide ester group which would cleave easily and link to an amine. This is shown in **Scheme 1.2.**



Scheme 1.2: Possible linking strategy between a fluorophore (Fl) containing an *N*-hydroxysuccinimide ester group and a photochromic molecule (PCA) containing an amino group to give Fl and PCA linked *via* an amide upon elimination of *N*-hydroxysuccinimide.

As the spectroscopic properties of the molecules would be important, the linker groups would have to be far enough away from the moiety in question in each case to not have any effect on the conjugation of the molecules, and the best way to do this would be to introduce the linker groups on the end of short aliphatic carbon chains, for example

1,3-propyl chains. If such linkers were in place on both the donor and acceptor molecules then the resulting linker chain between the two is shown in **Figure 1.5.**

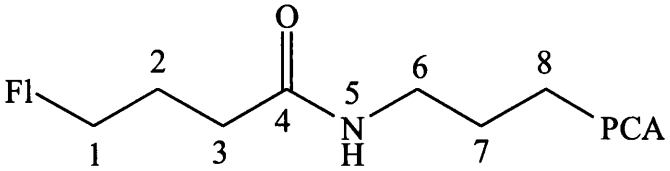


Figure 1.5: Length of proposed linkage between the fluorophore Fl and the photochromic acceptor PCA. The two 1,3-propyl chains are present to minimise interference of the linker group with the spectral characteristics of Fl and PCA.

It is possible to calculate the distance between a so linked donor and acceptor by considering the bond lengths and angles in the linker chain. The relevant bond lengths are shown in **Table 1.1**.[5]

Bond	Length/Å
C-C	1.54
C-N	1.47

Table 1.1: Relevant bond lengths.

From these data, and the knowledge that sp^3-hybridised atoms such as carbons 1-3 and 6-8, nitrogen 5 in **Figure 1.6** have a bond angle of roughly 109° and sp^2-hybridised atoms such as carbon 4 have a bond angle of 120°,[5] it is possible to calculate the distance between the donor and acceptor using trigonometry.

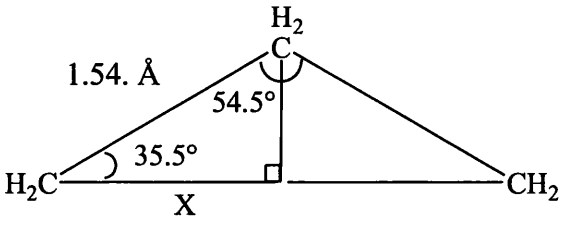


Figure 1.6: A trigonometric representation of an sp^3-hybridised C-C-C bridge.

For example, for the sp^3-hybridised atoms the distance can be worked out as follows: **Figure 1.6** shows a C-C-C fragment with bond angle 109° as a triangle, which can be divided into two right-angled triangles as shown.

Trigonometry can then be used to work out the length X in Å, which is equal to 1.54 x (cos 35.5) = 1.25 Å. The distance between the two lower CH_2 groups is therefore 2.50 Å. When similar calculations are made for the whole linker chain a donor-acceptor distance of 11.3 Å results, and if this linking strategy is used RET can be assumed to occur as long as the calculated Förster distance is larger than 11.3 Å

Therefore it was considered necessary to find a photochromic molecule that would absorb light at 426 nm in one form but not the other, and had spectroscopic characteristics that were such that the calculated value of R_0 for that molecule and **1** would be larger than 11.3 Å, assuming the linking strategy outlined above is used.

The first stage of the project was therefore to investigate the literature with the aim of finding a photochromic molecule that fit these criteria.

1.4 Photochromism.[6,7]

Photochromism is defined as "a reversible transformation between chemical species, induced in one or both directions by electromagnetic radiation, between two states having observable light absorptions in different regions."[6] This transformation is represented in **Figure 1.7**.

$$A(\lambda_1) \underset{h\upsilon_2 \text{ or } \Delta}{\overset{h\upsilon_1}{\rightleftharpoons}} B(\lambda_2)$$

Figure 1.7: Photochromism: The reversible conversion of a molecule (A – with a λ_{max} of λ_1 which corresponds to $h\upsilon_1$) to its isomer (B – with a λ_{max} of λ_2 which corresponds to $h\upsilon_2$) brought about in one direction by light ($h\upsilon$) and in the other direction by light or heat (Δ).

The initial species, which can be referred to as the "A-form" with an absorbance maximum λ_1, is usually thermally stable, meaning that the transition from A to the photoconverted "B-form" with an absorbance maximum λ_2, is brought about only by light. The B-form is rarely thermally stable, however, and thermal as well as photochemical back reactions are common in many organic photochromic species.

If the conversion from B to A is brought about by heat, the molecule is said to exhibit *T-type* photochromism. For T-type systems there is usually a photochemical back reaction as well, which can generally be demonstrated by the "bleaching" of the coloured

B-species by irradiation with light of the correct wavelength, but the thermal back reaction usually predominates. If the B to A reaction is exclusively photochemical the molecule is said to exhibit *P-type* photochromism and the B-form is considered to be thermally stable or thermally irreversible.

For many photochromic systems the A-form is colourless or pale yellow and the B-form is coloured. This is a consequence of the fact that the B-form absorbs light at a longer wavelength than the A-form ($\lambda_1 < \lambda_2$). When $\lambda_1 < \lambda_2$ the phenomenon is referred to as *positive photochromism*. Conversely, when $\lambda_1 > \lambda_2$ the phenomenon is referred to as *negative* or *inverse photochromism*, but this is less common due to the mechanism of most photochromic reactions. The absorption spectrum changes due to changes in the geometry and electron distribution of the system. For most photochromic compounds of interest to scientists there is a visible colour change involved, but neither the A-form nor the B-form need be coloured for a molecule to be classed as photochromic. The term can also apply to systems absorbing in the far ultraviolet or infra-red regions of the electromagnetic spectrum. The vast majority of known photochromic systems involve unimolecular photoconversions, which is much more convenient from a practical point of view than the much less common photochromic bimolecular photocycloaddition reactions.

Aside from the colour change, a photochromic transformation also involves changes in physical and chemical properties that occur alongside the more easily observed colour change. Such properties can include refractive index, conductivity, chelate formation, phase transitions, solubility and viscosity. The possible applications of photochromism can therefore be divided into two distinct categories: applications depending on the colour change and applications depending on the changes of other physical properties. Examples of the former would include photochromic lenses and novelty items such as T-shirts and toys, which represent the major commercial uses of photochromic compounds at the moment. Examples of the latter would include optoelectronic systems, holographic systems and information storage.[6,8]

Digital optical data storage in write-once compact disc form is now widely accepted as the most user-friendly and convenient information handling method available. There are many reasons for this, which include the increased robustness in comparison with magnetic recording media due to the non-contact laser reading method, the ready availability of cheap mass-produced diode lasers and the possibility of high storage

capacities.[8,9,10] The possible use of photochromic compounds in digital optoelectronic memory media and switching systems is the basis of modern research into photochromism done by such groups as those of Irie in Japan,[10] Feringa in the Netherlands,[8,9] Krongauz in Israel,[11] Yokoyama in Japan,[12] etc. P-type photochromic molecules are attractive from this perspective as they represent an easily and reversibly convertible 1 and 0 for binary information storage systems that can theoretically be read, written, erased and re-written indefinitely.[10] There are many advantages of developing organic photochromic compounds for this use, mainly the relative ease of fabrication and the ease and accuracy of "tuning" of physical properties of the molecules such as colour and conductivity by molecular engineering,[7] which in principle could yield a wide range of organic photochromic molecules. Another advantage is that any number of physical properties such as refractive index can be used non-destructively to detect the photochromic change and thereby read the stored information, as using the change in UV-Vis spectrum as a detection method would photochemically convert the species and thus erase the information, and is therefore classed as a destructive read-out method.[6]

In order for a photochromic compound to be useful in any application, be it sunglasses, novelty items or optoelectronic systems, it must possess several other properties besides the inherent bistability (the interconversion between two different forms of the molecule). The necessary criteria that are important in this respect are as follows.

1. No thermal interconversion between the isomers over a large temperature range: only P-type photochromism is desirable.
2. Both isomers should possess fatigue resistance: The photoconversion should occur many times without significant degradation through side reactions (10^5 cycles would make it comparable with magnetic storage techniques).[10]
3. Both forms should be easily detectible.
4. The detection procedure should be non-destructive, possibly involving refractive index or conductivity detection.
5. An efficient switching process would have high quantum yields in both directions.
6. Switching cycles should be fast: ps or quicker.
7. The compound should retain its properties when incorporated into such media as polymer matrices.

It is the development of photochromic molecules that satisfy all these criteria that drives research into organic photochromism.

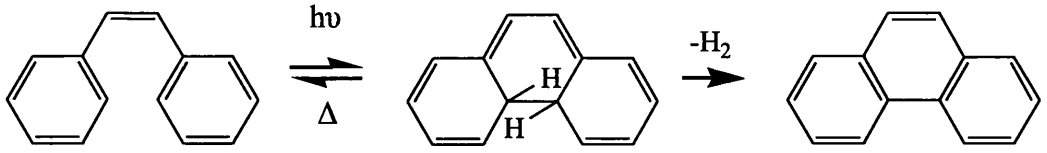
There are many families of organic photochromic compounds. Important families include spiropyrans[11] (the group of compounds that provided the starting point for research into photochromic memory media[13]), fulgides[12] (Heller's research into which yielded the first thermally irreversible photochromic compound), azoquinone compounds[14] and chromenes,[15] but these have no bearing on this project. This project specifically deals with photochromic diarylethenes, and these will be discussed in detail.

1.5 Photochromic diarylethenes.

1.5.1 *Development of photochromic diarylethenes.*

This section is a summary of the development of 1,2-diheteroarylethenes as an important family of photochromic molecules. The background work reported in this section is almost entirely the work of the group of Prof. Masahiro Irie in Kyushu University, Japan. That work is discussed in Prof. Irie's excellent 2000 review article.[10] The following section is a summary of the important points mentioned in that review.

The photochromism of 1,2-diarylalkenes is based on what was considered a side reaction in the photochemical *E-Z* isomerisation of stilbene; a photocyclisation of the 1,3,5-hexatriene moiety.[15] *Z*-Stilbene (**2**) was known to undergo reversible photocyclisation to form dihydrophenanthrene (**3**), which would in turn irreversibly lose hydrogen in the presence of air to form phenanthrene (**4**), gaining aromaticity.[16] This is shown in **Scheme 1.3**.



2 **3** **4**

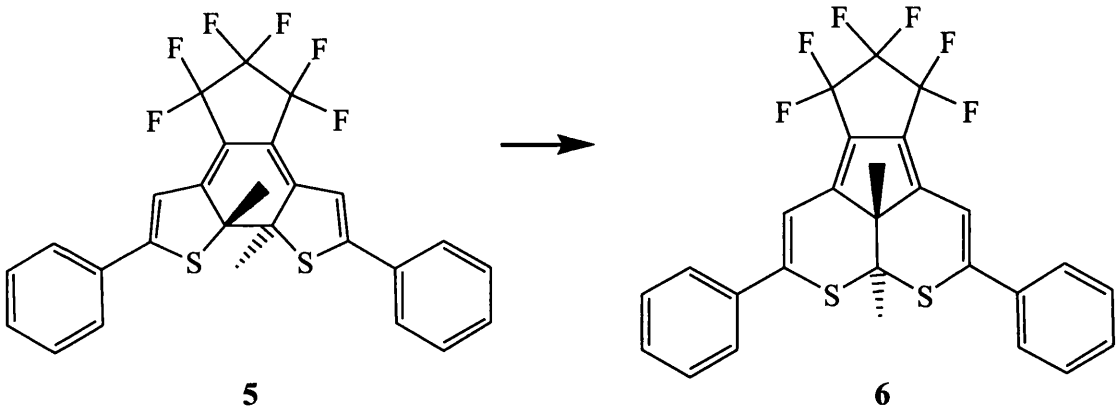
Scheme 1.3: The reversible conversion of *Z*-stilbene (2) to dihydrophenanthrene (3) and the subsequent elimination of hydrogen from 3 in the presence of air to form phenanthrene (4).[10,15]

In 1988 Irie *et al.* showed that if the two hydrogen atoms susceptible to elimination were replaced with methyl groups no elimination occurred and the photochromic

conversion between the stilbene and dihydrophenanthrene analogues became fully reversible.[17] Once the main research objective was regarded as utilising the photocyclisation rather than the *E-Z* photoisomerisation, the more common *E-Z* reaction became an undesirable side reaction, which can be suppressed by the addition of a cyclic system onto the ethene group.[10,17]

Diphenylcycloalkenes, however, are thermally reversible, and one of the main objectives in the early stages of this work was to make these photochromic compounds thermally irreversible. Work published by Kellogg *et al.* in 1967 showed that replacement of the phenyl groups of stilbene with thienyl groups increased the stability of the closed form.[18] The increase in thermal stability upon substitution with heteroaromatic rings can be explained in terms of the amount of aromatic stabilisation energy that is lost in the cyclisation process, as shown by Irie et al. in their 1988 theoretical study of several diarylethenes.[19] The energy barrier for the thermal cycloreversion reaction of 1,2-diphenylethene is very small because the destruction of the aromatic conjugation increases the ground-state energy of the closed form. The loss of aromatic stabilisation energy for 1,2-di(3-furyl)ethene is much less due to the different orbital energies of the furan ring, which means that the ground state energy of the difuryl compound is much lower and the energy barrier for the cycloreversion reaction is much higher. It was found that the closed forms of diarylethenes containing aryl groups with low aromatic stabilisation energies, e.g. thiophene, selenophene, furan and thiazole were stable indefinitely in the dark and that species containing pyrrole, indole and phenyl groups were not stable.[17] This evident thermal irreversibility is a huge advantage in the development of memories and switches based on photochromic diarylethenes.

The two biggest barriers to the fatigue resistance of diarylethenes are reaction with singlet oxygen in air to form endoperoxides and the irreversible reaction of the closed species in the absence of air to form the condensed ring structure **6** shown in **Scheme 1.4**. The reaction with singlet oxygen can be suppressed by using heterocyclic groups such as benzothiophene which are less reactive to singlet oxygen.



5 6

Scheme 1.4: The unwanted side reaction of the closed form (5) of a photochromic diheteroarylethene to form the unwanted by-product 6.[10]

Compound **6** was determined by X-ray crystallographic analysis to be the product of the main unwanted side-reaction of the process in the absence of oxygen. It was found that the introduction of methyl substituents onto the 4- and 4'- positions of the thiophenes prevented this cyclisation reaction. Diarylperfluorocyclopentenes show excellent fatigue resistance, as repeatable cycle numbers of more than 10^4 are common.

Diarylethenes exist in two conformations: the parallel conformation (in which the aryl groups are in mirror symmetry) and the antiparallel conformation (in which the two aryl groups are in C_2 symmetry). For typical diarylethenes the two conformations exist in a ratio of 1:1, and as the photocyclisation reaction can only proceed from the antiparallel conformation the cyclisation quantum yield for the ring-closure reaction can have a maximum value of 0.5. Quantum yields of up to and including 0.5 have been reported for diarylethenes, suggesting that all molecules that can convert do convert. Attempts to increase the population of the antiparallel form by introducing bulky substituents onto the aryl groups, placing diarylethenes in rigid polymer backbones and in the presence of β-cyclodextrins with appropriately sized cavities have served to increase the observed photocyclisation quantum yield greatly.

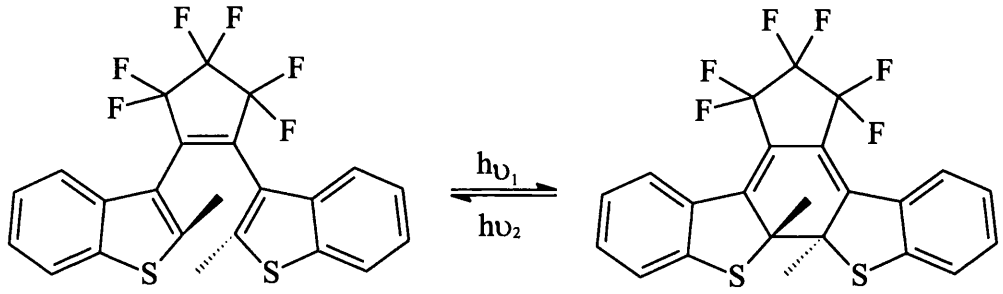
Work has also gone into reducing the cycloreversion quantum yield with the aim of allowing multiple readouts with the minimum amount of destruction of the closed form.

Experiments have taken place with different cycloalkenes. Diarylmaleic anhydrides and diarylmaleimides exhibit photochromic performance on a par with that of diarylperfluorocyclopentenes, the only difference being an increase in absorption wavelength, which is useful as an option in molecular design. Many diarylcyclopentenes have been synthesised by the group of Prof. B. L. Feringa in the Netherlands and their

photochromic performance has been compared with that of the corresponding perfluorocyclopentenes. It was found that the cyclopentene compounds are less fatigue resistant and have poor spectral splitting in comparison to perfluorocyclopentene derivatives.[20] The electron-withdrawing effect of the perfluoro moiety promotes the cyclisation reaction, improving the performance in comparison with cyclopentene derivatives.

Picosecond and femtosecond laser experiments have shown that the cyclisation and cycloreversion reactions of representative diarylethenes take place on the picosecond timescale, which fits the requirements for use in data storage.

The most widely used diarylethenes have a form similar to that shown in **Scheme 1.5,** 1,2-*bis*-(2-methylbenzo-[*b*]-thiophen-3-yl)perfluorocyclopentene (**7**).



Open form

7

Closed form

8

Scheme 1.5: The thermally irreversible photochromic conversion of the open form of a typical diarylperfluorocyclopentene (7) to its closed form (8).[10]

Diarylperfluorocyclopentenes tend to exhibit good spectral splitting between the open and closed forms. The closed form tends to absorb at a higher wavelength than the open form and these compounds therefore possess positive photochromic properties. Much work has gone into making diarylperfluorocyclopentenes with absorbances in the region of 650-830 nm as this would allow them to be converted using cheap diode lasers which is a requirement for uses in data storage.

As a conclusion to the notes on Irie's 2000 review, the thermal irreversibility, fatigue resistance, fast switching times and high photochromic quantum yields make photochromic diarylperfluorocyclopentenes ideal for many possible applications.

Since 2000 much work has gone into developing diarylperfluorocyclopentenes for uses in memory media. The Feringa group has reported many advances in photochromic

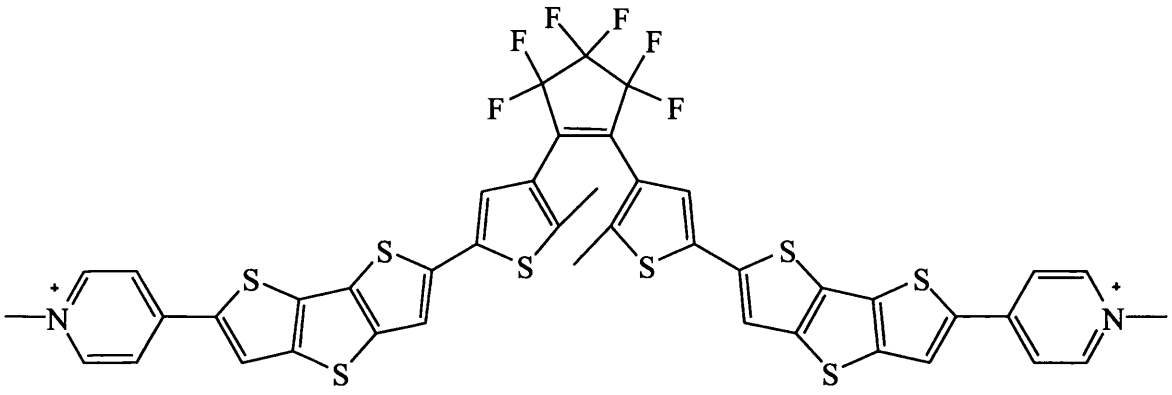
switches.[21] The Irie group has reported many new photochromic compounds,[22] the photochromism of single crystals of diarylethenes[23] and diarylethenes in an amorphous state as glass-like photochromic films.[24] Other groups such as those of Branda in Vancouver,[25] Kryschi in Nuremburg,[26] Krayushkin in Moscow,[27] etc. have published work in this area, dealing with such aspects as the detailed investigation of the photochromic reaction, development of photochromic polymers containing diarylethene units, etc.

1.5.2 Fluorescent diarylethenes.

In the course of work to develop diarylethenes for use in memories and switches there have been several papers published on the subject of using fluorescence as the non-destructive readout method. The Irie group has published reports of several diarylethenes that are fluorescent in the open form and non-fluorescent or weakly fluorescent in the closed form. This work was discussed in a review article by Matsuda and Irie in 2004,[28] along with other photoswitchable properties that could be useful for non-destructive readout methods such as conductivity and magnetism. Photochromic fluorescence modulation was also discussed in an article by Raymo *et al.* in 2005.[29] This section contains a brief summary of the work discussed in these reviews.

Earlier work into diarylethenes with photoswitchable fluorescence involved the synthesis of diarylethenes with fluorescent aryl groups that caused the diarylethenes themselves to exhibit fluorescence. An example of this is the molecule **9** shown in **Figure 1.8**, reported by Lehn in 1995, which is fluorescent in the open form and non-fluorescent in the closed form.[30]

Other photoswitchable fluorescent diarylethenes have been reported since 1995 by Irie,[31-34,41] Tian[35] and Kryschi[36] among others. Photoswitchably fluorescent fulgides have also been reported.[12] The synthesis of fluorescent diarylethene complexes with transition metal ions has also been reported by Branda,[37] Lehn,[38] Tian[39] and others. More information about this area can be found in the two articles mentioned above, as can information about other photoswitchable properties that will not be discussed here.



9

Figure 1.8: The fluorescent A-form of a photoswitchable fluorescent diarylperfluorocyclopentene (9) as reported by Lehn in 1995.[30] The closed form was not fluorescent.

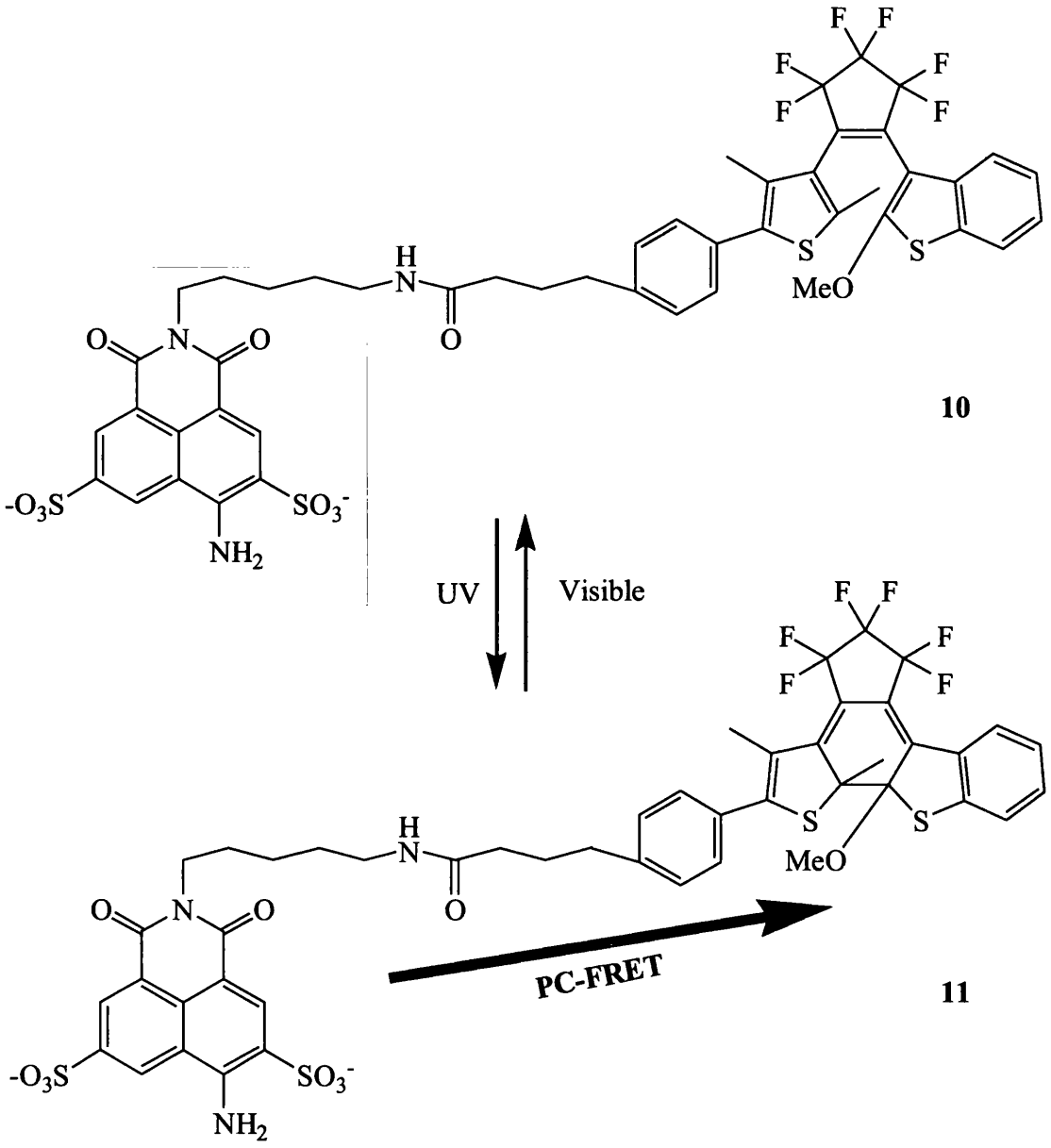
1.5.3 PC-FRET.

Of particular relevance to this project is the emergent field of PC-FRET. Several papers have been published in which a fluorescent molecule has been linked to a photochromic molecule as a switchable acceptor for RET. The technique has been given a name; Photochromic Fluorescence Resonance Energy Transfer, or PC-FRET for short and was developed as a method for the quantitative determination of RET for use in the repeatable monitoring of molecular interactions.[40,41] This work has been undertaken by the Jovin group in the Max Plank Institute for Biophysical Chemistry in Göttingen, Germany in collaboration with the Irie group, and it is discussed by Matsuda and Irie in their 2004 review[28] and Raymo *et al.* in their 2005 article.[29]

Successful PC-FRET involving Lucifer Yellow cadaverine (LYC) as the donor linked to a photochromic diarylperfluorocyclopentene as the photoswitchable acceptor was reported in 2002.[41] An example of this is given in **Scheme 1.6**, but the synthesis and performance of several molecules are reported in the paper.

As can be seen in **Scheme 1.6** the linking strategy employed to join the donor to the acceptor was similar to the proposed linking strategy described in **Scheme 1.2** and **Figure 1.5**. In order to synthesise the linked molecule the LYC donor containing an amino group was reacted with the photochromic acceptor containing an *N*-hydroxysuccinimide ester to give the donor-acceptor molecule **10** which is linked *via* an amide group. The molecule was designed by selecting the photochromic acceptor molecules, which have closed forms that absorb light in the range of 540-570 nm and then selecting LYC as the donor that

best suited the photochromic acceptor molecules, i.e. with an emission spectrum that overlapped the absorption spectrum of the closed form but not the open form of the acceptor. The linking strategy was designed based on R_0 calculations so that the donor-acceptor distance would fall well within the Förster distance, and the molecules were then synthesised.



Scheme 1.6: The photochromic reaction and consequent switching of energy transfer of a PC-FRET capable molecule as reported by Jovin in 2002.[40]

After experimental confirmation that the photochromic behaviour of the acceptor was not affected by the linking with the donor, the donor-acceptor behaviour of the system was studied. It was found that energy transfer can be switched reversibly by

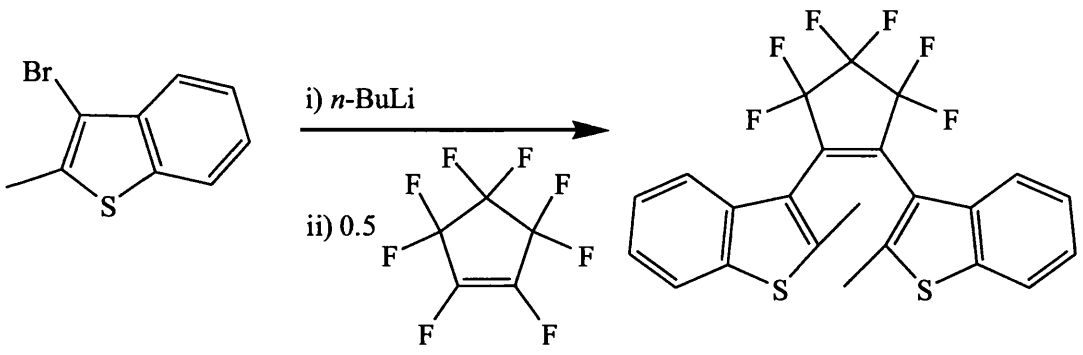
photoconverting the diarylethene acceptor as shown by the simultaneous reduction in the emission intensity of the donor and the presence of the closed-form absorbance band upon irradiation. RET efficiencies were calculated to be almost 100 % for the best examples and were found to be dependent on the chain length of the linker group. This work shows that PC-FRET is a viable process.

The Jovin group has published several more papers concerning FRET since 2002, involving an overview of the field[42] and the reporting of novel molecules and applications.[43,44] Other examples of PC-FRET have been reported including the use of protein-bound photochromic spiropyrans to quench quantum dot photoluminescence,[45] a diarylethene linked *via* an adamantyl group to an anthracene fluorophore[33b] and PC-FRET between a spiropyran acceptor and fluoroscein.[46]

It can be seen that not only is the idea of photoswitchable fluorescence *via* the use of a photochromic acceptor viable, but also that it is an idea that is the basis for an area of research that has emerged very recently.

1.5.4 Synthesis of photochromic diarylethenes.

Diarylperfluorocyclopentenes are generally synthesised by the reaction of metalated heterocycles with octafluorocyclopentene (**13**), which has excellent reactivity towards nucleophiles at the double bond due to the electron-withdrawing effect of the fluorine atoms.[47] The synthesis of **7**, which is a typical synthesis of this type of compound, is shown in **Scheme 1.7.**[48]



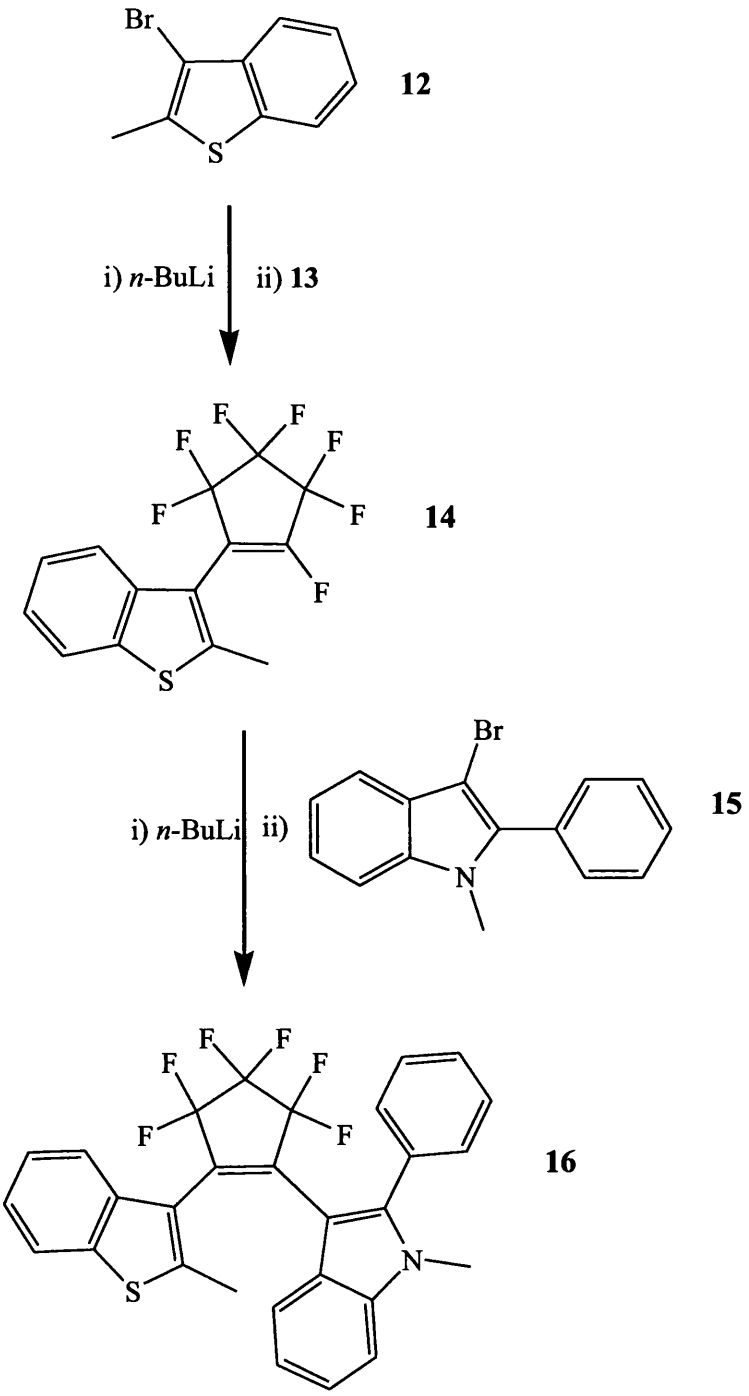
12 **13** **7**

Scheme 1.7: A typical synthesis of a symmetrical photochromic diarylperfluorocyclopentene (7).[48]

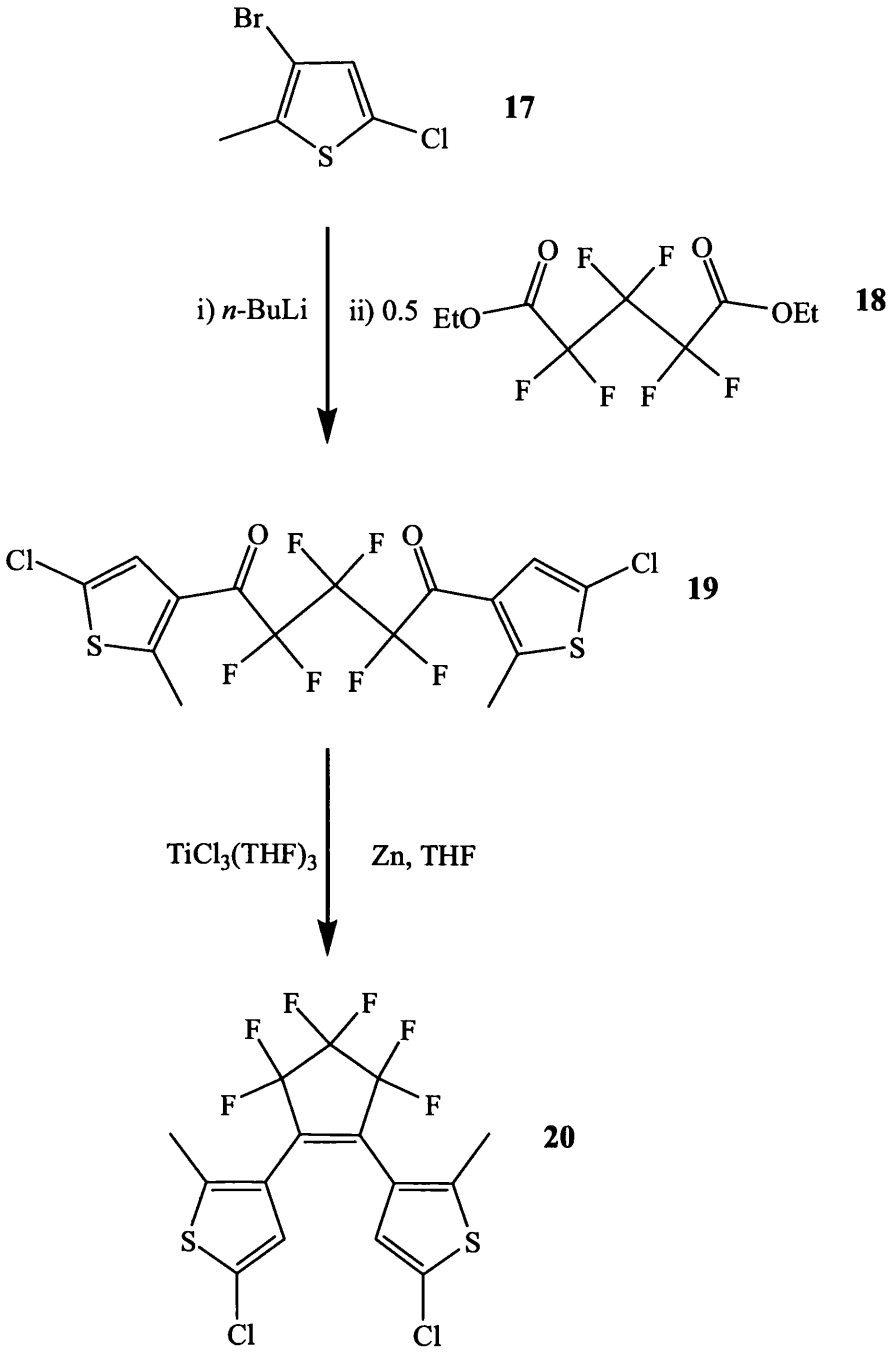
The one-step disubstitution reaction shown in Scheme **1.7** is useful for the production of symmetrical diarylperfluorocyclopentenes. Unsymmetrical diarylperfluorocyclopentenes can be prepared simply by reacting **13** with one mole equivalent of one metalated heterocycle (e.g. **12**) to produce a monosubstituted perfluorocyclopentene (e.g. **14**) and then reacting that with one mole equivalent of another metalated heterocycle (e.g. **15**) to produce the unsymmetrical product (e.g. **16**), as shown in **Scheme 1.8**.[25]

This reaction has been used to synthesise a wide variety of photochromic diarylperfluorocyclopentenes.[10]

This method does, however, suffer from low to moderate yield and the relatively high cost of the starting material octafluorocyclopentene.[10] With this in mind, in 1999 Lucas *et al.* of the Feringa group published an alternative method of synthesis of symmetrical photochromic diarylperfluorocyclopentenes. This method involved the bromine-metal exchange of 2-methyl-3-bromo-5-chlorothiophene (**17**) and subsequent reaction with the ethyl ester of hexafluoroglutaric acid (**18**) to form the diketone **19** which then underwent ring-closure by intramolecular titanium-mediated McMurry coupling to form the photochromic diarylperfluorocyclopentene **20**. This reaction is shown in **Scheme 1.9.**[49]



Scheme 1.8: A typical synthesis of an unsymmetrical photochromic diarylperfluorocyclopentene (16).[10,25]



Scheme 1.9: Alternative synthesis of a symmetrical diarylperfluorocyclopentene (20).[10,49]

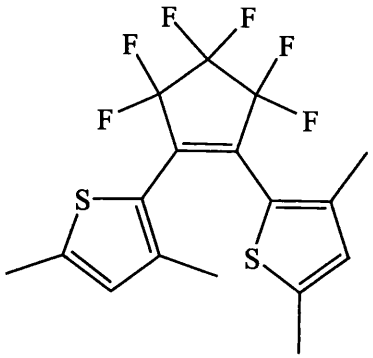
1.6 Selected acceptor molecule.

As mentioned previously, the objective of this project was to design and synthesise a photochromic molecule that has a B-state λ_{max} of as close to 426 nm (the fluorescence emission wavelength of *N*-methylacridone) as possible and contains an amino linker group. This project outline could be broken down into several specific targets. The targets were as follows.

a) Either design or find in the literature a suitable photochromic molecule.
b) Synthesise the photochromic molecule and evaluate the theoretical viability of the proposed donor-acceptor system. This would involve calculation of the theoretical spectral overlap integral and the critical separation of the proposed donor-acceptor system.
c) Design a linkable photochromic target molecule and a synthetic route to that target.
d) Carry out the total synthesis of the linkable photochromic molecule.

1.6.1 *1,2-bis(3,5-dimethyl-2-thienyl)perfluorocyclopentene.*

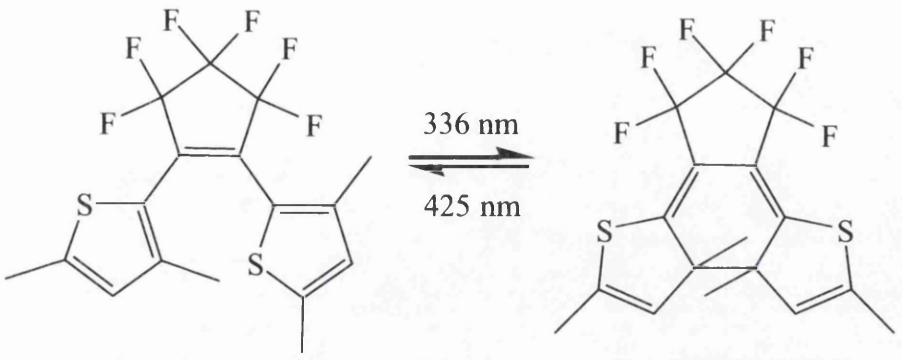
After a thorough search of the extant literature concerned with photochromism the ideal molecule was found in a paper written by members of the Irie group published in *Chem. Comm.* in 1995.[50] The photochromic acceptor molecule, 1,2-*bis*(3,4-dimethyl-2-thienyl)perfluorocyclopentene (**21**) is shown in **Figure 1.9.**



21

Figure 1.9: The selected photochromic acceptor molecule: 1,2-*bis*(3,4-dimethyl-2-thienyl)-perfluorocyclopentene (21).[50]

The photochromic conversion of the open form **21** to the closed form **22** is shown in **Scheme 1.10**, and the superimposed absorption spectra of the two forms are shown in **Figure 1.10.**



21 **22**

Scheme 1.10: The thermally irreversible photochromic conversion of 21 to 22.[50]

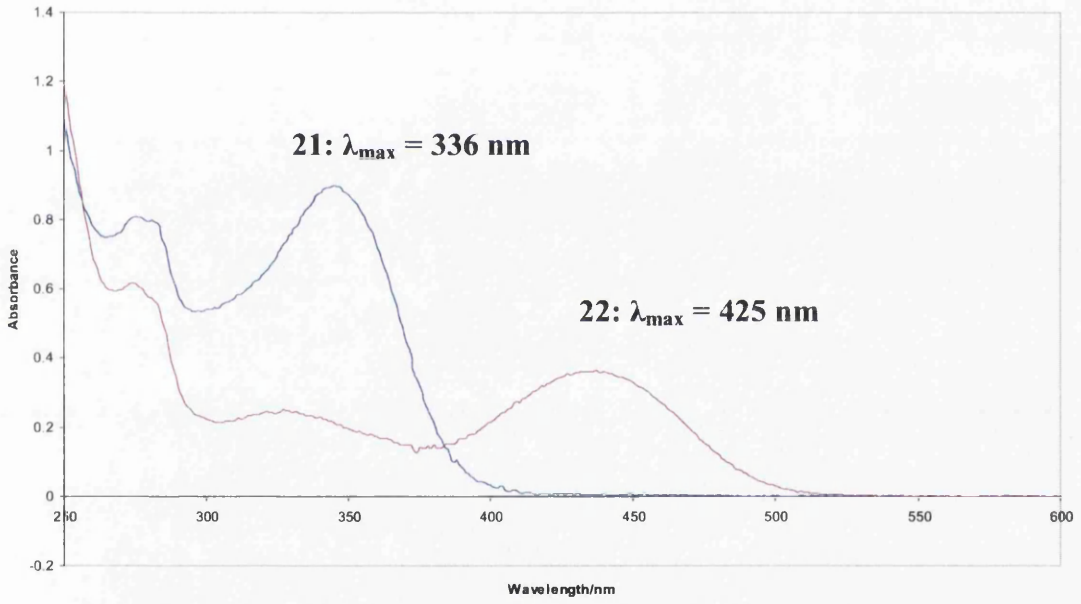


Figure 1.10: Superimposed absorption spectra of molecules 21 & 22 (cf. Scheme 1.10), illustrating the change in absorption characteristics brought about by the photochromic reaction.[50]

Molecule **21** was reported to have an open form λ_{max} of 336 nm ($\varepsilon = 1.3 \times 10^4$ $dm^3mol^{-1}cm^{-1}$ $\Phi_{A\rightarrow B} = 0.40$) and **22** a closed form λ_{max} of 425 nm ($\varepsilon = 5.8 \times 10^3$ $dm^3mol^{-1}cm^{-1}$ $\Phi_{B\rightarrow A} = 0.58$) in hexane.

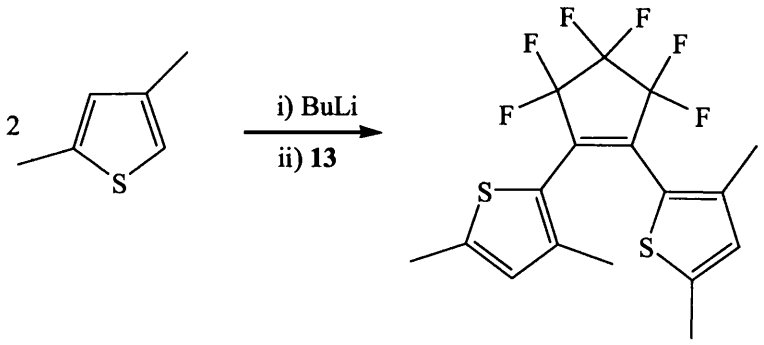
The absorbance maximum of the closed form **22**, 425 nm (in hexane), is exactly right for the application in question. Also, as it is part of the diarylethene family it possesses all

of the qualities that make diarylethenes so promising for many applications. The compound has been reported to be thermally stable (stability is defined as having a lifetime exceeding 12 hours at 80 °C[10]), and to have a repeatable cycle number of over 4 x 10^3 times in air, making it highly fatigue resistant and thermally irreversible.[10] High quantum yields ($\Phi_{A\rightarrow B} = 0.40$, $\Phi_{B\rightarrow A} = 0.58$) have been reported for the photochemical interconversion reactions,[50] which are useful for application as a photoswitchable acceptor.

Compound **21** was also the only appropriate candidate discovered for the required use. Very few examples of photochromic molecules in the literature have absorbance maxima at such low wavelengths. This is because, as mentioned before, most of the molecular design work relating to these compounds has served to lengthen the absorbance wavelengths of the compounds in order to convert them with cheap diode lasers for use in recording media.[10] The only reason this molecule was developed was that the closed form is yellow, a colour needed for any multicoloured display.[50]

1.6.2 Synthesis of 1,2-bis(3,5-dimethyl-2-thienyl)perfluorocyclopentene (21).

The literature synthetic route as reported by Irie is shown in **Scheme 1.11.**[50]



23 **21**

Scheme 1.11: Literature synthesis of molecule 21 (cf. Scheme 1.7) as reported by Uchida and Irie in 1995.[50]

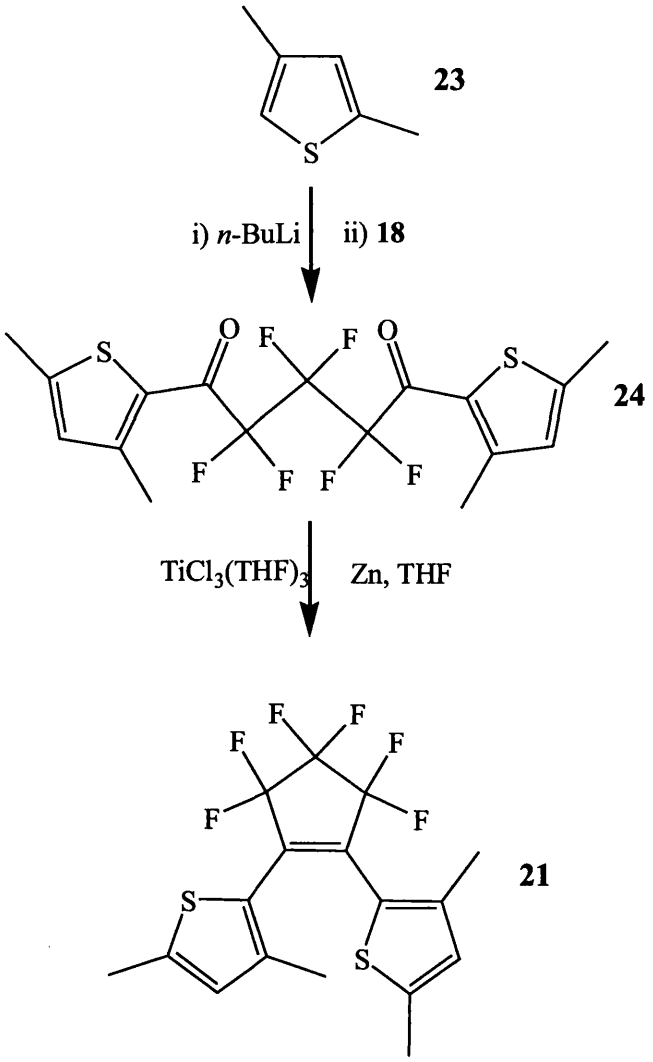
This synthesis is theoretically attractive. As mentioned earlier it is a method that has been used many times to make many new photochromic diarylperfluorocyclopentenes. Practically there are problems with the above method. Compound **13** is relatively expensive (£154 for 25 g from Lancaster) and volatile (boiling points from 15 °C to 25 °C have been reported), which makes it difficult to handle and measure accurately.

Apparently because of the difficulty of handling the starting material the yields have been reported to be generally low, with a large amount of the monosubstituted perfluorocyclopentene being formed.[10] The difficulty of handling octafluorocyclopentene also makes the reaction difficult to carry out on an industrial scale, although this has little bearing on this project. The method also involved 2,4-dimethylthiophene (**23**) as the heterocyclic starting material. This is important as **23** lithiates exclusively at the 5-position adjacent to the heteroatom and this leads to the 5-substitution of the thiophene ring on to the perfluorocyclopentene. The site of substitution on the thiophene and resultant alteration of the conjugation of the system is the reason for the lower absorbance wavelength, as the analog of the closed form **22** that features 3-substitution on **23** has been shown to absorb at a higher wavelength than **22**.[50]

1.6.3 Possible alternative synthesis.

A theoretical synthesis of **21** using Lucas' alternative route is given in **Scheme 1.12.** This specific synthesis is a modification of published syntheses by this method and has not been reported in the literature.

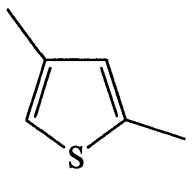
The alternative route starts with hexafluoroglutaric acid, which can be esterified with ethanol in the presence of acid to give **18**, which can be reacted with lithiated **23** to give the diketone **24**, which can be cyclised to form the photochromic molecule. Hexafluoroglutaric acid is much cheaper than octafluorocyclopentene (£64.30 for 25 g. Aldrich) and much easier to handle as it is a solid. Compound **23** is, again, essential as a starting material for this method.



Scheme 1.12: Possible alternative route to 21 (cf. Scheme 1.9).

1.6.4 *The need for 2,4-dimethylthiophene.*

The starting material, 2,4-dimethylthiophene, (**23, Figure 1.11**) is, as has been said, essential for the synthesis of the target molecule.



23

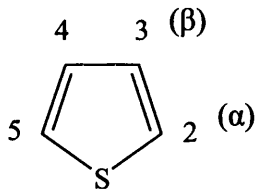
Figure 1.11: 2,4-Dimethylthiophene (23).

Both methyl groups are vitally important to the synthesis and function of the photochromic target molecule. The 2-methyl group blocks a potentially favourable lithiation site and forces lithiation to the required 5-position. The 4-methyl group becomes important in the photochromic function of the molecule as it prevents elimination of H_2 from the closed form of the molecule in the presence of air to form an aromatic phenanthrene analog (cf. **Scheme 1.3**), a reaction that, as mentioned previously, is common in stilbenes and is highly favourable due to the production of an aromatic product.

Compound **23** is not commercially available. Furthermore, it was discovered that published syntheses of **23** are uniformly inconvenient, due to low yields, low selectivity, unavailable starting materials, prohibitively harsh reaction conditions or a combination of these. This was a surprising discovery for what seemed to be such a simple molecule, and leads to the natural question, "why is this the case?"

In order to attempt to answer this question, and to present the thinking behind the approach that was eventually taken in tackling this problem, it is necessary to give some background to thiophenes in general and **23** in particular.

1.7 Thiophene.



25

Figure 1.12: Thiophene (25 - showing positions on the ring described with numbers starting from the heteroatom in position 1, and also described as α- and β-positions in relation to the position of the heteroatom).

Viktor Meyer discovered thiophene (**25**, **Figure 1.12**), in 1882 as a contaminant of benzene obtained from coal tar.[51]

The name thiophene was coined in reference to the similarities of thiophene to benzene in terms of some chemical and physical properties such as smell, boiling point and reactivity. The similarity to benzene comes about due to the similarity of the outer electrons of the sulfur atom to those of the –HC=CH- group, and thiophene is therefore analogous to benzene in terms of electron distribution. Substituents in the 2-and 5-

positions experience σ-electron withdrawing and a π-electron donating effect from the sulfur heteroatom which has an effect on the reactivity of thiophene.[51-54]

Thiophene is more stable than pyrrole and furan, and this is attributed to the larger bonding radius of sulfur, which decreases ring strain due to larger bond angles.[51-54]

Thiophene derivatives are important building blocks in many areas of chemistry such as pharmaceuticals,[55] conductive polymers,[56,57] liquid crystals[58] and, of course, photochromic molecular switches to name but a few.

1.7.1 Reactivity of thiophene.

The presence of the sulfur atom in the heteroaromatic ring has a large effect on the reactivity of thiophene and its derivatives, and the resulting differences in reactivity between thiophene and benzene have formed the basis of research into thiophenes since the Meyer era. An example of the difference is that thiophene is 10^3 to 10^5 times more reactive than benzene toward electrophiles.[53]

Thiophene is known to undergo a wide range of electrophilic substitution reactions, although its increased stability in relation to other 5-membered heterocycles means it is less reactive than those compounds. Thiophene is known to be 10^2 times less reactive than furan and 10^7 times less reactive than pyrrole, although quantitative reactivities vary considerably with different reactions.[54] Because of its greater stability thiophene is not as easily cleaved by acids as furan.

Electrophilic substitution can occur at either possible ring position, but electrophiles attack preferentially at the α- or 2-position due to the larger degree of stabilisation of the intermediate involved in 2-substitution than the intermediate involved in 3-substitution. In fact, studies have shown that reaction at the 2-position of thiophene is around 1000 times more favourable than reaction at the 3-position, although this can vary to about 100 times with different electrophiles.[53]

Reaction of thiophene with organolithium reagents results in exclusive lithiation at the 2-position, this time due to the electron-withdrawing effect of the heteroatom. 2-Metalated thiophenes react readily with electrophiles to form 2-substituted thiophenes.[54]

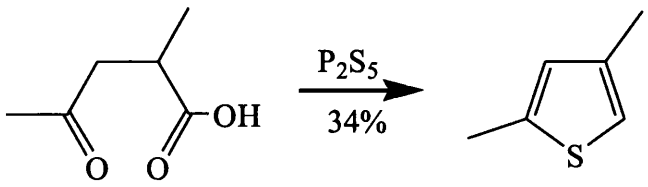
1.8 Syntheses of 2,4-dimethylthiophene.

For such an apparently simple molecule, a literature search reveals a surprising paucity of syntheses of 2,4-dimethylthiophene, and all the published syntheses, as has been mentioned before, have major flaws that would preclude their use in the production of starting materials if a more convenient alternative could be found. These flaws include low yields, unavailable starting materials, inconveniently harsh reaction conditions etc.

Examples of published syntheses of **23** are given below, along with reasons why the syntheses were considered unsuitable.

1.8.1 Ring-closure syntheses.

The first reported synthesis of **23** was reported by Zelinsky in 1887 and involved the ring-closure reaction of α-methyllevulinic acid (**26**) with phosphorus pentasulfide.[59] This method is shown in **Scheme 1.13.**



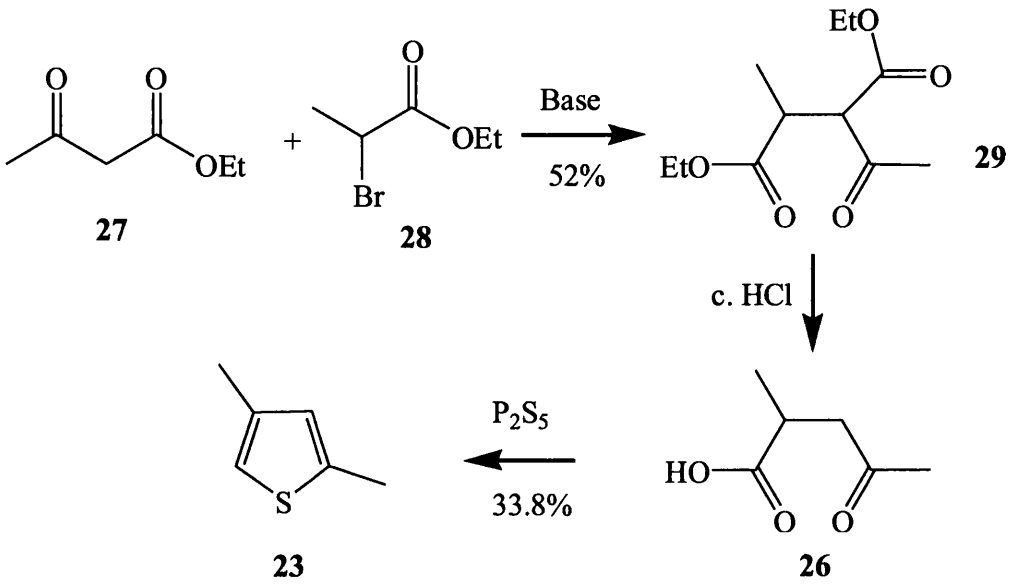
26 **23**

Scheme 1.13: The synthesis of 2,4-dimethylthiophene *via* the ring-closure reaction of α-methyllevulinic acid (26), as reported by Zelinsky in 1887.[59]

The Zelinsky method is low-yielding and the starting material, **26,** is not commercially available. Even though this is the classic method of synthesis it proved undesirable because of the need to synthesise the starting material.

The Zelinsky synthesis was used by Nishimura and Mizutani in 1975 as part of their work on identifying thiophenes formed by the photolysis of sulfur-containing amino acids in flavour deterioration of onion and garlic flavours.[60] Compound **26**, which was not commercially available then either, had to be synthesised. The reported synthesis started with condensation of ethyl acetoacetate (**27**) and ethyl 2-bromopropionate (**28**) to give ethyl 2-methyl-3-ethoxycarbonyl-4-oxopentanoate (**29**), which was then hydrolysed and decarboxylated with concentrated hydrochloric acid to give **26**. The preparation of the

starting material was low yielding, as was the subsequent ring-closure reaction. The full synthesis of **23** as reported by Nishimura is given in **Scheme 1.14.**



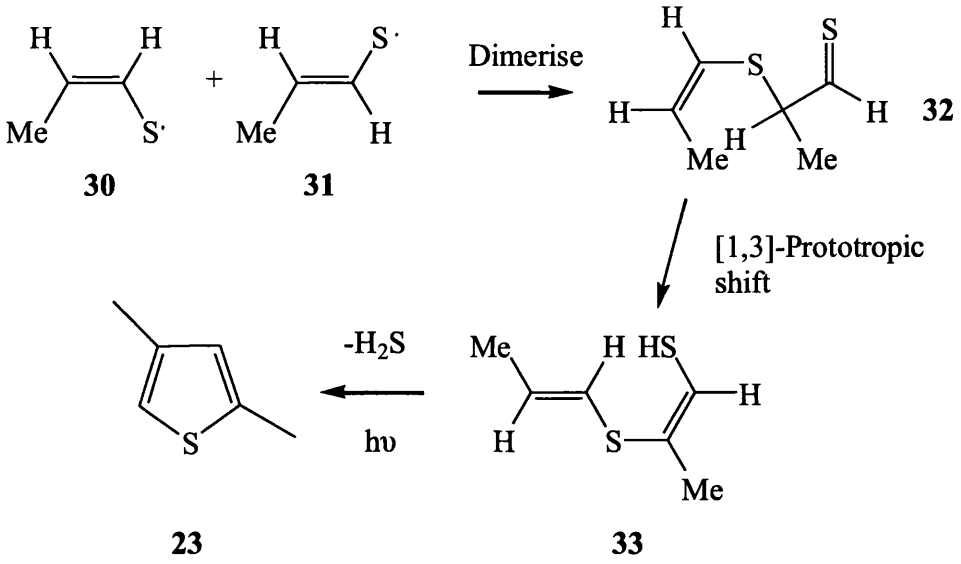
Scheme 1.14: The synthesis of 23 following the Zelinsky method (cf. Scheme 1.13) but including the two-step synthesis of *α*-methyllevulinic acid (26), as reported by Nishimura in 1975.[60]

This method, although viable, suffers from the low yield of both the synthesis of the starting material and of the product and the relative inconvenience of the synthesis.

This method would, however, be a suitable method for the synthesis of **23** if no other could be found. There is no guarantee that this method would be suitable for the synthesis of other functionalised 2,4-disubstituted thiophenes, however.

Nishimura's investigations revealed that 2,4-dimethylthiophene was one of the major products of UV irradiated *S*-(*cis*-1-propenyl)-L-cysteine ($CH_3CH_2CH_2SCH_2CH(NH_2)COOH$ – a precursor of onion and garlic flavours), and it was probably formed by two isomers of a 1-propenylthiyl radical **30** & **31** (formed from the cysteine) reacting together to form unstable dimeric thioaldehyde **32**, which undergoes a [1,3]-prototropic shift to give α,β-unsaturated thiol **33**. This compound then eliminates H_2S to give stable **23**. This is shown in **Scheme 1.15.**

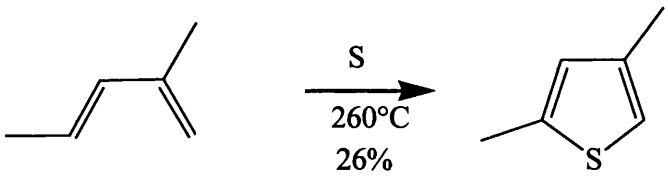
Nishimura *et al.* succeeded in preparing **33** in low yield. While irradiation did give **23**, thus validating the proposed reaction shown in **Scheme 1.15**, the low yield and relative complexity of this route means it is not a viable path for synthesising **23** for the purposes of this project.



30 31 32 33 23

Scheme 1.15: The natural production of 23 as a flavour compound in onions as reported by Nishimura in 1975.[60]

The Zelinsky method was used by Hartough in 1951 as part of his acylation studies into the thiophene and furan series.[61] The older method was used alongside a newer ring-closure method which involved heating 2-methyl-1,3-pentadiene (**34**) with sulfur at 260 °C for two and a half hours. This method is shown in **Scheme 1.16**.



34 23

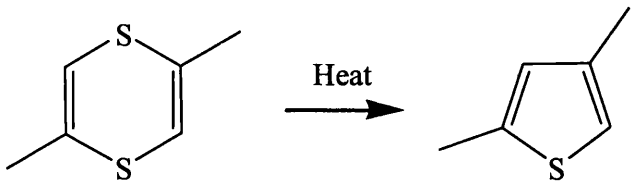
Scheme 1.16: Synthesis of 23 *via* the ring-closure reaction of 2-methyl-1,3-pentadiene (34) with elemental sulfur as reported by Hartough in 1951.[61]

This method is also very low yielding, and inconvenient due to the high temperatures required for the reaction and the use of the starting material **34** that, although commercially available, is very expensive and can only be obtained in small quantities. All these factors would serve to limit the amount of product that could be made and so it was prudent to search for other methods of synthesis. This method would also possibly not be suitable for the synthesis of a range of other 2,4-disubstituted thiophenes.

1.8.2 Other methods.

In 1952 Parham *et al.* reported the production of **23** by the thermal decomposition of 2,5-dimethyl-1,4-dithiadiene (**35**).[62] This was of an investigation of the chemical behaviour of heterocyclic vinyl ethers. The reaction is shown in **Scheme 1.17.**

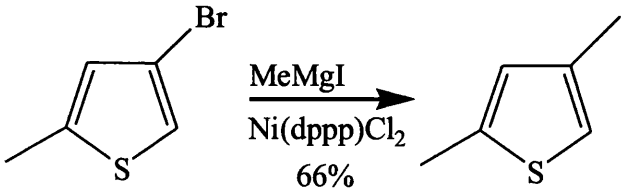
This is a very low-yielding method and the synthesis of the starting material consists of four steps. In addition to this the structure of the product assumed to be **23** was not rigorously confirmed. This method was thus not considered viable.



35 **23**

Scheme 1.17 Synthesis of 23 by the thermal decomposition of 2,5-dimethyl-1,4-dithiadiene (35) as reported by Parham in 1952.[62]

Compound **23** was synthesised by Takeshita *et al.* in 1991 by the reaction of 4-bromo-2-methylthiophene **36** with methylmagnesium iodide.[63] The reaction is shown in **Scheme 1.18**.



36 **23**

Scheme 1.18: Synthesis of 23 as reported by Takeshita in 1991.[63]

This is a convenient and high-yielding method. The method was not chosen as the final method of synthesis for several reasons. Firstly, the starting material **36** was not commercially available at the time the work was carried out. However, 4-bromo-2-methylthiophene was introduced as a product by Aldrich in August 2004, and is now therefore easy to obtain. Secondly, this synthesis can only produce 2-methylthiophenes and as will be seen later on it became necessary to synthesise a range of 2-substituted 4-methylthiophenes in order to advance the project.

Methods that give **23** as part of a large range of products or as a side-product have not been discussed, although several do exist.[64]

1.8.3 Lithiation of 3-methylthiophene.

Sicé reported the method that was chosen as the most promising in 1954.[65] The procedure that he used is quoted below.

> "*4-Methyl-2-thenaldehyde* (II). 3-methylthiophene (29 g) was added at room temperature, in a slow stream, to a solution of butyllithium (0.33mole) in 500 mL of ether. The reaction was exothermic and it proceeded with evolution of gas. The mixture was stirred for two additional hours and then slowly added (45min) to an ice-cold solution of dimethylformamide (30 mL, 0.39mole) in ether (100 mL). The yellow suspension was stirred overnight and then poured onto ice. The solvent layer was washed with water, dilute hydrochloric acid, aqueous sodium bicarbonate and again with water. The dried solution was concentrated. The residue distilled as a colourless liquid (25.6 g, 61 %). [Characterisation data are reported]. The hydrazone of II decomposed at 120 °C in a solution of potassium hydroxide in ethylene glycol to give an 85% yield of 2,4-dimethylthiophene."

This method was used by Boelens *et al.* in 1971 during their work to identify volatile flavour compounds in onions.[66] As has been previously mentioned, **23** is found in onion and garlic flavourings. This work led to the work by Nishimura that was previously described.[60] This method was also used by Collins *et al.* as recently as 2002 as the first step in a multi-step synthesis.[55c] Even though Sicé made no mention of this, the subsequent papers that reference his work report that the synthesis is not selective, and significant quantities of 2,3-disubstituted thiophene are produced when the method is used. It was thought, however, that it would be possible to improve the selectivity of the method due to the extensive amount of work involving the selective lithiation of heterocycles that has been done in the Centre for Clean Chemistry.[67] In order to do this it was necessary to understand the more general reactions of the starting material, 3-methylthiophene, and other 3-substituted thiophenes.

1.9 Reactions of 3-substituted thiophenes.

1.9.1 Electrophilic substitution reactions of 3-substituted thiophenes.

3-Substituted thiophenes will give predominantly 2,3-disubstituted products upon reaction with electrophiles if the 3-substituent is electron donating, for example an alkyl substituent. This is the case for 3-methylthiophene, which is always predominantly substituted in the 2-position.[68] This is due to the α-directing effect of the sulfur and the inductive effect of the 3-methyl group.[69]

This effect is counteracted when the alkyl substituent in the 3-position is relatively bulky.[68] The dominance of 2-substitution is reduced with increased bulkiness of the 3-substituent,[70] and in the case of 3-*tert*-butylthiophene substitution is directed to the 5-position almost exclusively.[71]

The dominance of 2-substitution can also be lessened when bulky electrophiles are used. In one paper published by Meth-Cohn in 2000 a variety of increasingly bulky Vilsmeier and Rieche formylating reagents were applied to 3-methylthiophene and although the 2-substitution always predominates the relative amount of 5-substitution can be seen to increase with increasing bulkiness of the formylating reagent.[72] This effect was also observed in Friedel-Crafts acylations.[69,73]

1.9.2 Lithiation reactions of 3-substituted thiophenes.

The fact that lithiation of thiophene is completely α-selective was discovered by Gilman in 1949.[51-54,74] The pronounced difference in the acidity of the 2- and 3-positions in thiophenes has been attributed to the activating effect of the adjacent sulfur atom making the α-position much more able to stabilise a negative charge, and thus making the α-hydrogen much more acidic.[75]

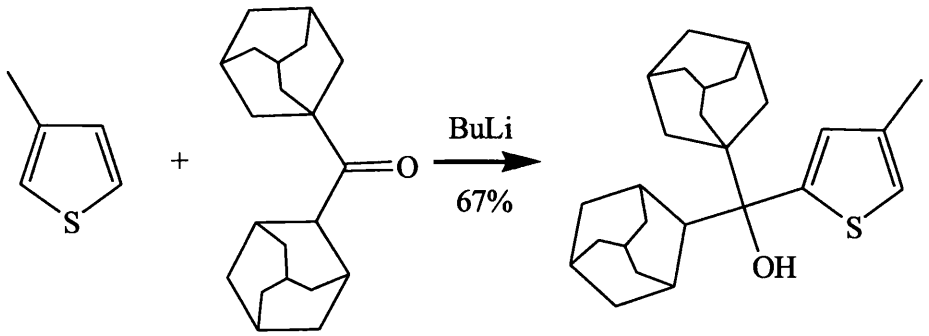
Lithiation with butyllithium is thought to start with the coordination of the lithium cation with the lone pair of electrons on the sulfur atom of the thiophene. This is followed by deprotonation of the most acidic neighbouring α-proton by the butyl carbanion, and finally by the substitution of the lithium metal in the place of the abstracted proton. For thiophene itself both α-protons are interchangeable, but for substituted thiophenes the proton that is most readily removed is determined by substituent effects.[51-54,74]

For 3-substituted thiophenes with a substituent that directs metalation α- to itself, such as a dimethylaminocarbonyl, dimethylaminomethyl or methanethiyl group, lithiation is directed to the 2-position, which is α- to the substituent and α- to the thiophene sulfur atom. This can be seen to be the result of a chelation effect whereby both the thiophene sulfur and the other coordinating centre, for example sulfur or nitrogen, coordinate to the lithium cation and the proton in the middle of the two centres is abstracted.[74,76]

For 3-substituted thiophenes with a substituent that does not direct metalation, for example 3-methylthiophene, lithiation occurs at both the 2- and 5-positions, but the 5-position usually predominates.[68,74] This effect was observed in the previously mentioned papers by Boelens *et al.*[66] and by Collins *et al.*[55c]

Similarly to electrophilic substitution reactions the predominance of the 5-position can be increased by increasing the size of the 3-substituent.[68,74] When 3-methylthiophene is lithiated with *n*-butyllithium the ratio of 5:2-substitution has been reported to be 80:20, but the ratio for 3-isopropylthiophene is 95:5 and for 3-*tert*-butylthiophene lithiation is almost exclusively 5-selective.[68]

Lithiation with a more sterically demanding organolithium reagent has also been shown to increase the predominance of lithiation in the 5-position; When TMEDA was added to the reaction mixture as a complexing agent for *n*-butyllithium the ratio was increased, although not dramatically.[68,74,79] It has also been reported that highly hindered electrophiles such as diadamantyl ketone (**37**) give solely 5-substituted products when reacted with lithiated 3-methylthiophene (**38**).[55d,77] This reaction is shown in **Scheme 1.19**.[77]

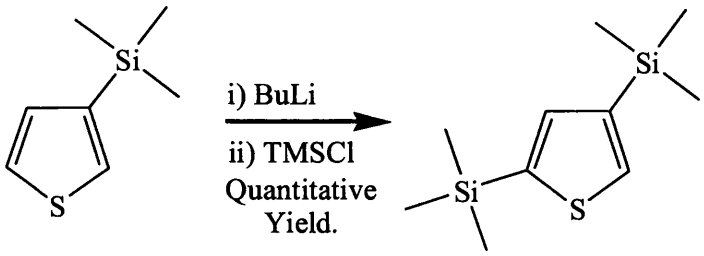


38 **37** **39**

Scheme 1.19: Reaction of 3-methylthiophene (38) with the bulky electrophile diadamantyl ketone (37) *via* lithiation to give only the 2,4-disubstituted product 39 as reported by Lomas in 1999.[77]

The low to moderate yields in these reactions suggest that the selectivity of the lithiation reaction is not affected and the highly hindered electrophile simply does not react with the 2-lithiated thiophene and that starting material is regenerated from the unreacted lithiated starting material upon workup.

There is also an example of the lithiation of 3-trimethylsilylthiophene (**40**) with butyllithium and reaction with trimethylsilyl chloride as an electrophile to produce 2,4-ditrimethylsilylthiophene (**41**) selectively, which shows the effect of both a bulky substituent and a bulky electrophile. This was reported by O'Donovan *et al.* in 1994 and is shown in **Scheme 1.20**.[78]

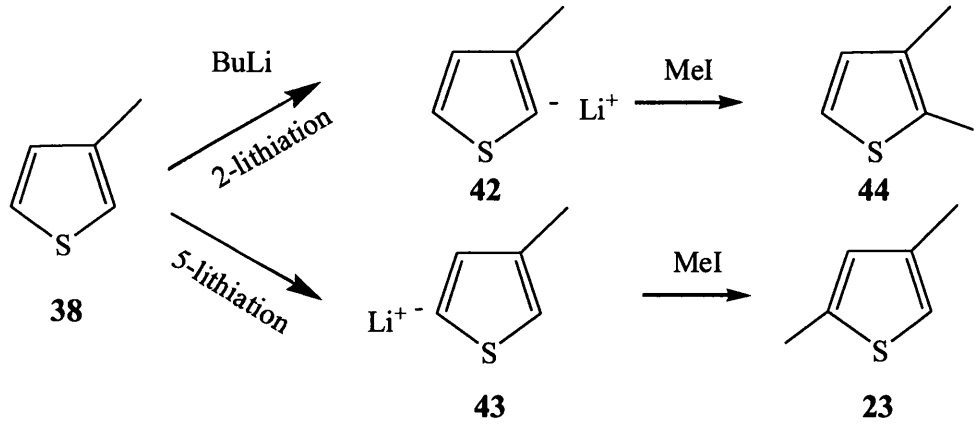


40 **41**

Scheme 1.20: The reaction of 3-trimethylsilylthiophene (40) with trimethylsilyl chloride *via* lithiation to produce 2,4-ditrimethylsilylthiophene (41) selectively, as reported by O'Donovan *et al.* in 1994.[78]

Given this background into the lithiation of thiophenes, this method was considered the most promising method for the synthesis of **23**. The formation of the aldehyde and subsequent reduction carried out by Sicé was considered a possibly superfluous reaction step. The most convenient reaction would involve lithiating **38** exclusively in the 5-position and reacting the resulting thienyllithium with iodomethane to produce **23**. This was not achievable initially because of the poor selectivity of the lithiation reaction. This is represented in **Scheme 1.21.**

According to previous literature reports **38** would be lithiated at both the 2- and 5-positions, with a preference for the 5-position to give the two thienyllithiums **42** and **43** shown above. The major product, (4-methyl-2-thienyl)lithium (**43**) would react with iodomethane to form the desired product **23** and the minor product (3-methyl-2-thienyl)lithium (**42**) would react similarly to form the unwanted product 2,3-dimethylthiophene (**44**). This reaction would need to be modified in order to increase the selectivity. This modification was therefore considered to be essential to the early stages of the project.

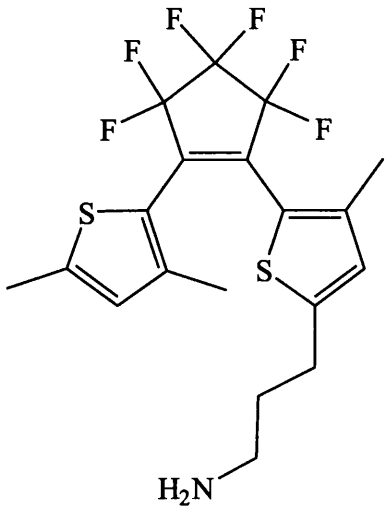


Scheme 1.21: The lithiation of 38 with butyllithium to produce (3-methyl-2-thienyl)lithium (42) which would theoretically react with iodomethane (MeI) to produce the minor product 2,3-dimethylthiophene (44) and (4-methyl-2-thienyl)lithium (43) which would theoretically react with iodomethane to produce the major product 23.

The previously mentioned importance of steric effects was considered to be the key to improving the reaction. Bulky electrophiles and bulky 3-substituents have been shown to direct lithiation in the right direction, but in this case both substituents are as unhindered as possible. Changing the lithiating reagent was considered the key to this and would form the first stage of this project, the results of which are reported in Chapter 2.

1.10 Proposed linkable acceptor molecule.

As an appropriate photochromic acceptor molecule had been found in the literature, the next stage was to decide on a modification strategy for the creation of a linkable version of that molecule. As mentioned previously, an amino group would be a useful linker, and adding the amino group to the molecule on the end of a propyl chain would not in principle alter the photochromic performance of the molecule, although this would have to be confirmed upon synthesis of the target. With this in mind a linkable version of the photochromic acceptor was designed. The proposed linkable photochromic acceptor molecule, 1-([3-methyl-5-(3-amino-1-propyl)]-2-thienyl)-2-(3,5-dimethyl-2-thienyl)perfluorocyclopentene (**45**) is shown in **Figure 1.13.**



45

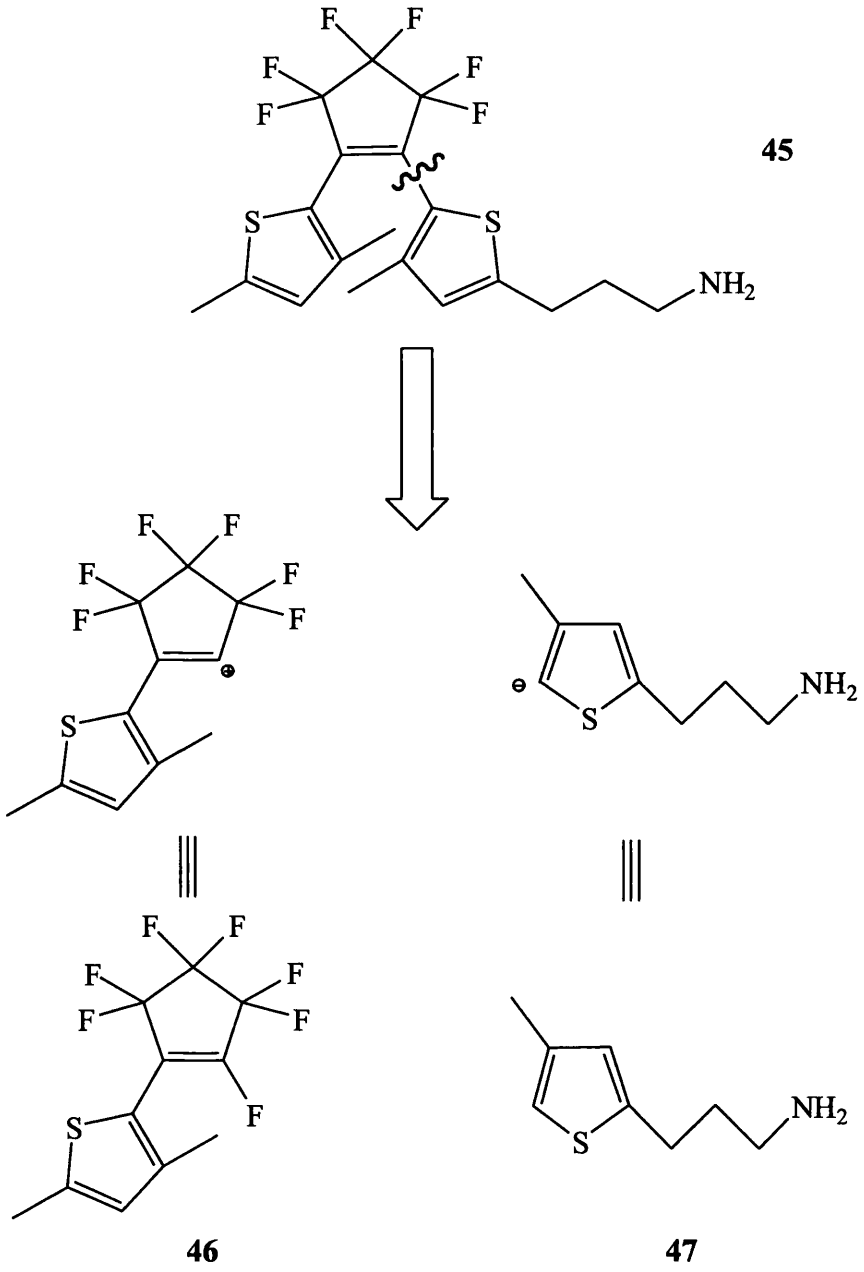
Figure 1.13: The proposed linkable photochromic acceptor molecule 1-([3-methyl-5-(3-amino-1-propyl)]-2-thienyl)-2-(3,5-dimethyl-2-thienyl) perfluorocyclopentene (45).

As mentioned previously, the synthesis of unsymmetrical perfluorocyclopentenes is relatively straightforward: perfluorocyclopentene (**13**) is reacted with one equivalent of one lithiated aryl reagent to give a monosubstituted perfluorocyclopentene and then this product is reacted with one equivalent of another lithiated aryl starting material to give the final unsymmetrical perfluorocyclopentenes, as shown in **Scheme 1.8.**

Disconnections of the target molecule are given in the following section.

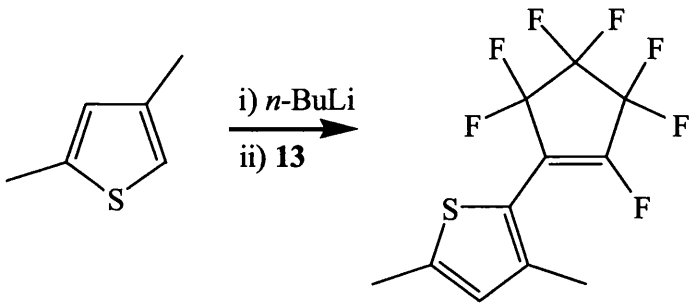
1.11 Disconnection of 45: Thienylpropylamine.

One possible disconnection of **45** is shown in **Scheme 1.22.**



Scheme 1.22: Disconnection of 45 to give the possible starting materials 1-(3,5-dimethyl-2-thienyl)perfluorocyclopentene (46) and 3-(4-methyl-2-thienyl)-1-propylamine (47).

The synthesis of 1-(3,5-dimethyl-2-thienyl)perfluorocyclopentene (**46**) was reported by Uchida and Irie in their 1995 paper[50] and is shown in **Scheme 1.23**.



23 **46**

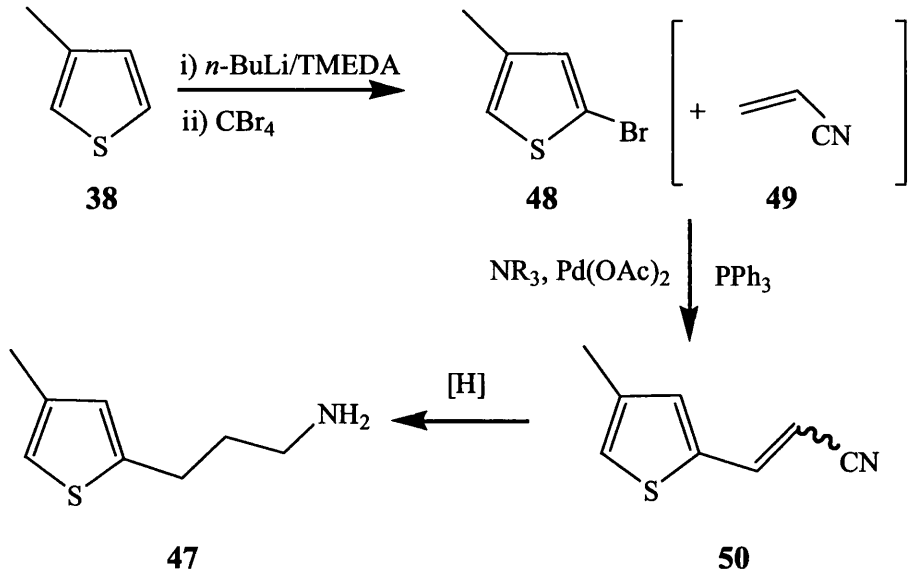
Scheme 1.23: Synthesis of 46 from the lithiation of one mole equivalent of 23 and reaction with 13 (cf. Scheme 1.8) as reported by Uchida and Irie in 1995.[50]

Compound **23** is lithiated with butyllithium and added to one mole equivalent of **13** to give **46**. Compound **46** would act as an electrophile in the same way as perfluorocyclopentene, but in only the one halogenated position on the double bond due to the electron withdrawing effect of the perfluoro moiety and the fluorine atom.[47,50] Uchida and Irie then went on to react **46** with a further mole equivalent of **23** to give **21**.[50]

The disconnection shown in **Scheme 1.22** shows the other starting material that could potentially be used for the synthesis of the final molecule, and that is 3-(4-methyl-2-thienyl)-1-propylamine (**47**). This compound has not been reported in the literature. Two possible synthetic routes to this molecule were designed.

1.11.1 *Proposed synthesis of 47: Heck coupling.*

The first proposed synthesis of **47** is shown in **Scheme 1.24.**



Scheme 1.24: Proposed synthesis of 47 *via* selective lithiation of 38 with BuLi and N, N, N', N'-tetramethylethylenediamine (TMEDA) and reaction with carbon tetrabromide to form 2-bromo-4-methylthiophene (48) as reported by Consiglio in 1982.[79] This would be followed by the Heck coupling of 48 with acrylonitrile (49) to form 3-(4-methyl-2-thienyl)acrylonitrile (50) which would be reduced to form 47.

The first step of the reaction involves a regioselective lithiation similar to that involved in the planned synthesis of compound **23.** Consiglio *et al.* reported the synthesis of 2-bromo-4-methylthiophene (**48**) with 93% selectivity in 1982 using *n*-butyllithium/ TMEDA as the lithiating reagent and carbon tetrabromide as the electrophile.[79] This route takes into account the steric effect on the selectivity of lithiation of **38** that was discussed in Section 1.9.2.

A possible problem for this reaction would be the known susceptibility of **38** to electrophilic bromination in the 2-position with a variety of brominating agents,[68,80] which would work against the selectivity of the reaction toward substitution at the 5-position. The aim of this step would be to find reaction conditions that support substitution at the 5-position over the 2-position, lending weight to the need for a general method of regioselective 5-substitution of 3-methylthiophene.

The second step in the reaction is a Heck coupling of **48** with acrylonitrile (**49**) in the presence of palladium acetate, a trialkylamine (e.g. triethylamine or tri-*n*-butylamine) and

triphenylphosphine to give 3-(4-methyl-2-thienyl)acrylonitrile (**50**) . This specific reaction has not been reported in the literature.

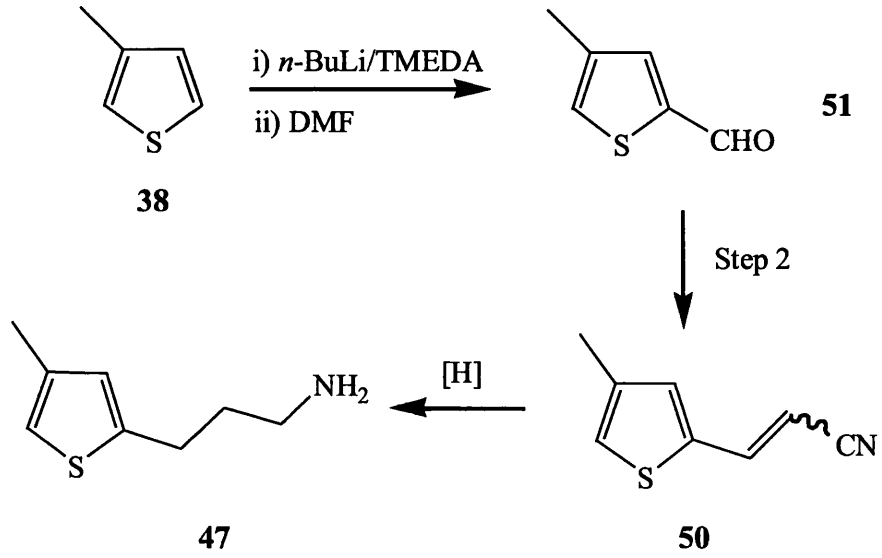
The Heck reaction was reported by Heck and Dieck in 1974,[81] and has since been widely reported and reviewed.[82] There have also been many reported examples of successful high-yielding Heck couplings of heteroaryl bromides and **49**.[83]

The ideal third step of this synthesis would involve the one-pot total reduction of the acrylonitrile group of **50** to give **47.** This specific reaction has not been reported in the literature but such total reductions, while rare, have been reported. High-yielding reductions of α,β-unsaturated nitriles have been reported using lithium aluminium hydride in diethyl ether,[84,85] sodium borohydride/cobalt chloride,[86] hydrogen and Raney nickel in ethanol/ammonia[87] and hydrogen in the presence of platinum oxide.[88]

Conjugate reductions are more common.[85,89] This would necessitate the subsequent reduction of the nitrile group, which could be achieved with sodium borohydride/cobalt chloride, [86] diborane,[90] tetrabutylammonium borohydride,[91] lithium aluminium hydride,[92] hydrogen in the presence of palladium,[93] etc.

1.11.2 Proposed synthesis of 47: aldehyde.

The second proposed synthesis of **47** is shown in **Scheme 1.25.**

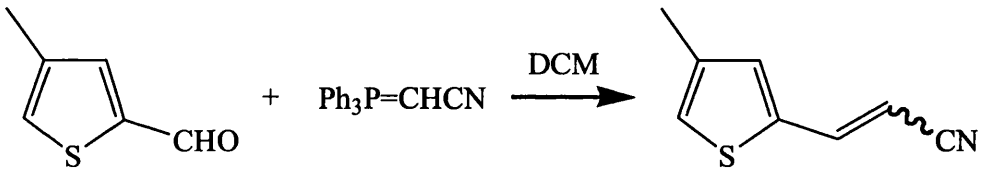


Scheme 1.25: Proposed synthesis of 46 *via* selective lithiation of 37 and reaction with *N,N*-dimethylformamide (DMF) to form 4-methyl-2-thiophenecarboxaldehyde (51) followed by olefination to form 3-(4-methyl-2-thienyl)acrylonitrile (50) which would be reduced to form 47.

As in Section 1.11.1 the first step of this synthesis would again involve the regioselective 5-substitution of **38**, but in this case the lithiated species would be reacted with *N,N*-dimethylformamide (DMF) to produce 4-methyl-2-thiophenecarboxaldehyde (**51**), which has been reported before by Sicé,[65] Detty (as a mixture of products of a poorly selective lithiation step),[70] Collins (also as the major product of a poorly selective lithiation)[55c] and Meth-Cohn (as one component in a mixture of formylation products).[72] The reaction of organolithium compounds with DMF to form aldehydes is a very common one[65,70,94] and if selectivity can be adequately achieved in the lithiation step this reaction should be viable.

The second step, the conversion of heterocyclic aldehyde **51** to heterocyclic acrylonitrile **50** could be carried out *via* the Wittig reaction, the Horner/Wadsworth/Emmons reaction or by the Knoevenagel-type reaction with cyanoacetic acid in the presence of base.

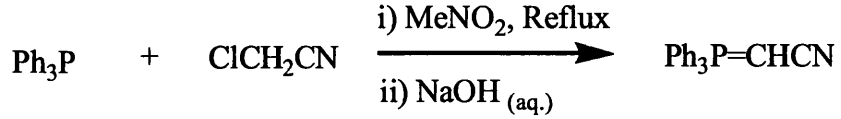
The proposed Wittig synthesis of **50** from the reaction of **51** with (triphenyl-λ^5-phosphanylidene)acetonitrile (**52**) is shown in **Scheme 1.26**.



51 **52** **50**

Scheme 1.26: Proposed Wittig reaction of 51 with (triphenyl-λ^5-phosphanylidene) acetonitrile (52) to form 50.

The ylid **52** can be conveniently prepared from triphenylphosphine (**53**) and cyanoacetonitrile (**54**), as is shown in **Scheme 1.27**.[95]

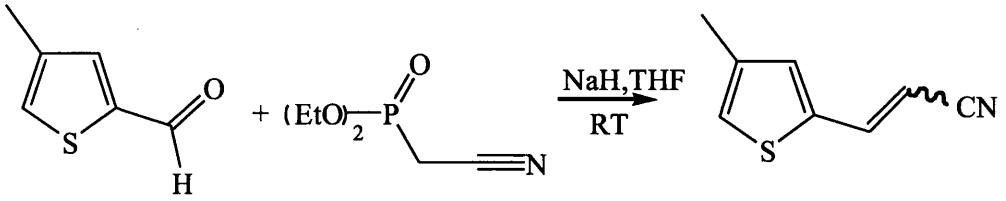


53 **54** **52**

Scheme 1.27: The synthesis of 52 by i) reaction of triphenylphosphine (53) and chloroacetonitrile (54) to form the hydrochloride salt and ii) reaction with aqueous sodium hydroxide to form 52.

Heteroaromatic aldehydes such as the aldehyde in question **51** are known to undergo Wittig reactions in high yields to give the corresponding acrylonitriles.[95,96]

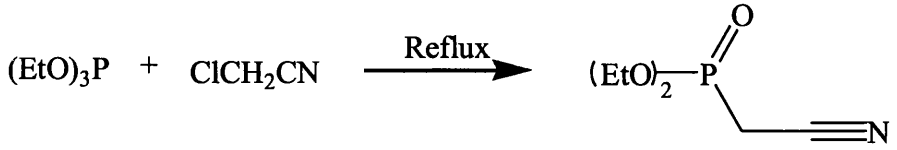
The proposed Horner/Wadsworth/Emmons synthesis of **50** from the reaction of **51** with diethylcyanomethylphosphonate (**55**) is shown in **Scheme 1.28.**



51 **55** **50**

Scheme 1.28: Proposed Horner/Wadsworth/Emmons reaction of 51 with diethylcyanomethylphosphonate (55) in the presence of sodium hydride to form 50.

This reaction is a modification of the Wittig reaction in which the carbanion produced when a phosphonate is deprotonated with a base such as sodium hydride reacts with a carbonyl group.[97] The phosphonate **55** can be synthesised *via* the neat Arbusov reaction of triethyl phosphite (**56**) and chloroacetonitrile (**54**) as shown in **Scheme 1.29**.[98]

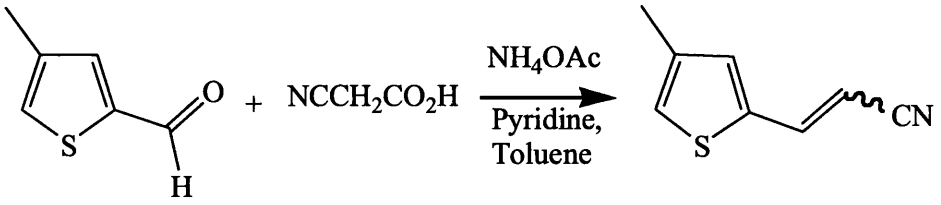


56 **54** **55**

Scheme 1.29: The neat Arbusov reaction of diethyl phosphite (56) with 54 to form 55.

The Arbusov reaction is carried out neat under reflux and tends to give high yields. The phosphonate product can be easily purified simply by distillation from the reaction vessel.[98] Aromatic aldehydes such as **51** are known to undergo Horner/Wadsworth/Emmons reactions conveniently and in high yields.[85d,99]

The proposed synthesis of **50** from the reaction of **51** with cyanoacetic acid (**57**) is shown in **Scheme 1.30.**



51 **57** **50**

Scheme 1.30: Knoevenagel-type reaction of 51 with cyanoacetic acid (57) in pyridine and toluene the presence of ammonium acetate (NH_4OAc) to form 50.

The Knoevenagel-type olefination of aldehydes with cyanoacetic acid in the presence of base is a moderately common reaction in the literature.[99a,100] Yields are usually high but reaction times are long.

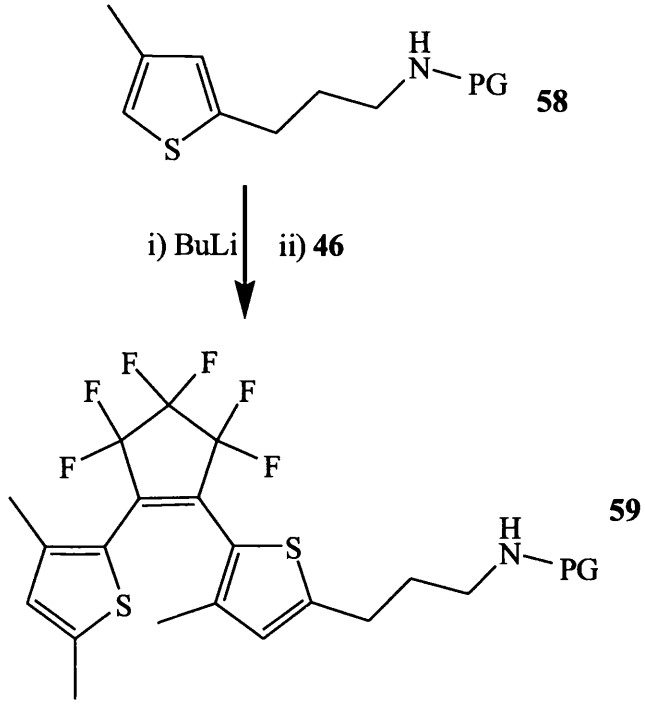
All the above reactions are feasible options for the synthesis of **50** from **51.** Compound **50** could then be reduced to **47** using the methods discussed in Section 1.11.1.

1.11.3 Proposed protection and reaction of 47.

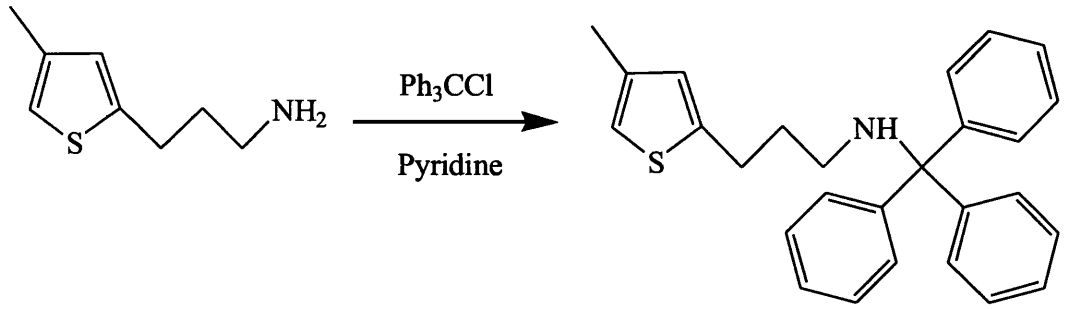
Organolithium reagents deprotonate amines readily.[101] It would therefore be necessary to protect the amine functionality of **47** with a protecting group (PG) before attempting to lithiate the heterocycle and reacting it with **46** (cf. **Scheme 1.8**). A general description of the final necessary reaction is shown in **Scheme 1.31**. The generic protected amine **58**, protected with a PG that is stable to organolithium reagents, should theoretically be lithiated at the 5-position of the thiophene ring in a similar way to **23** and would therefore react with **46** to form the generic protected amine **59**, which would yield the target molecule **45** upon deprotection.

As alkyllithiums are such powerful reagents it is difficult to find protecting groups that are stable to them. The triphenylmethyl (trityl) protecting group is known to be stable to strong bases and has been known to show some stability in the presence of organolithium reagents.[102,103] This group is also highly sterically hindered,[104] which in the present case may serve to block the protected amino functionality against attack by organolithium reagents.

Compound **47** should be protected with the trityl group by addition of the amine to triphenylmethyl chloride in pyridine[105] or triethylamine[106] to give the protected amine **60**. This proposed reaction is shown in **Scheme 1.32.**



Scheme 1.31: Proposed lithiation of 47 protected with PG, a base-stable protecting group (58) and reaction with 46 to form 59, the protected version of 45 (cf. Scheme 1.8).



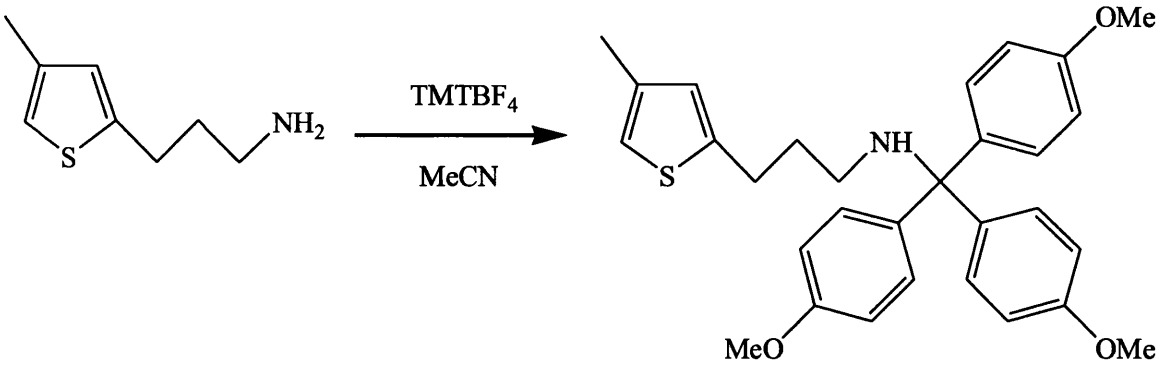
47 **60**

Scheme 1.32: Proposed protection of 47 with the triphenylmethyl (trityl) group *via* reaction with triphenylmethyl chloride (Ph_3CCl) in pyridine to give the trityl-protected amine 60.

After reaction of the protected amine the trityl group can be removed with by refluxing with concentrated hydrochloric acid or trifluoroacetic acid.[105]

The parent trityl group is known to be difficult to remove from an amino functionality, but trityl groups with methoxy substituents are easier to remove, requiring less harsh reaction conditions, while still retaining stability to bases.[107,108]

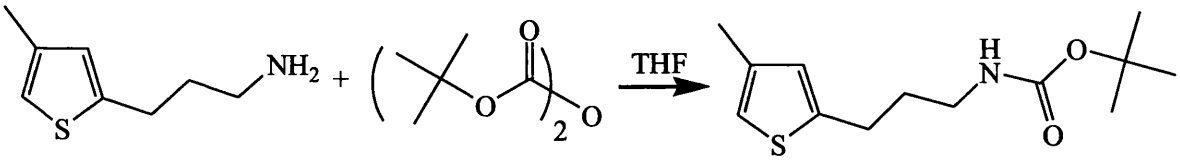
Compound **47** should be protected with the 4,4',4''-trimethoxytrityl (TMT) group by reaction with 4,4',4''-trimethoxytrityl tetrafluoroborate ($TMTBF_4$ – made by reacting 4,4',4''-trimethoxytrityl alcohol with fluoroboric acid in acetic anhydride) in acetonitrile.[107,108] The proposed reaction to form the TMT-protected amine **61** is shown in **Scheme 1.33.** The presence of the methoxy groups may present a problem for the final reaction as they may direct lithiation onto the methoxyphenyl groups.



47 **61**

Scheme 1.33: Proposed protection of 47 with the trimethoxytrityl (TMT) group *via* reaction with 4,4',4''-trimethoxytrityl tetrafluoroborate ($TMTBF_4$) in acetonitrile to give the trityl-protected amine 61.

The *tert*-butoxycarbonyl (Boc) protecting group, which is a very common protecting group,[109-112] is also a possibility. Compound **47** could be protected with the Boc group by reaction with di-*tert*-butyl dicarbonate (Boc anhydride, **62**) to give the Boc-protected amine **63** as shown in **Scheme 1.34.**



47 **62** **63**

Scheme 1.34: Proposed protection of 46 with the *tert*-butoxycarbonyl (Boc) group by reaction of 47 with di-*tert*-butyl dicarbonate (62) in THF to form the Boc-protected amine 63.

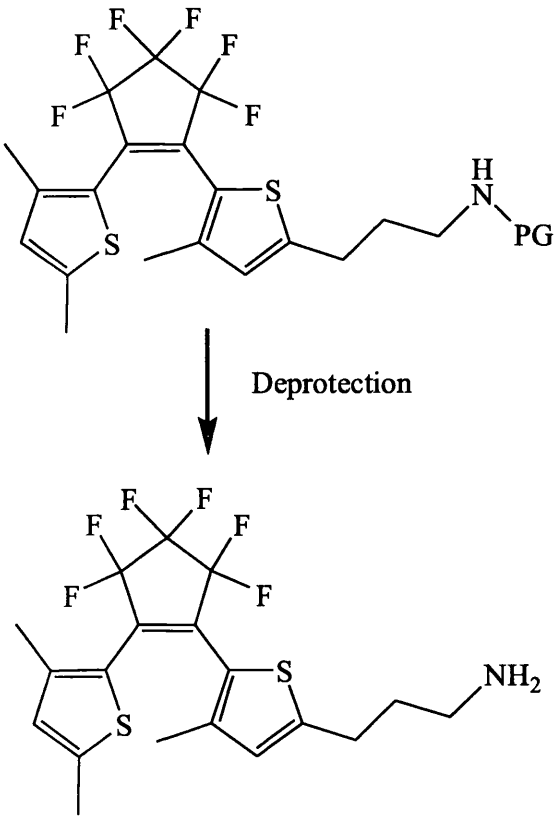
There are examples in the literature of Boc-protected amines undergoing electrophilic substitutions with organolithium reagents[113] and Boc-protected amines with halogen functionalities undergoing halogen-lithium exchange reactions[114] without compromising

the Boc group, and this gives a good indication that the group might be stable in deprotonation reactions with an organolithium reagent.

Boc protecting groups are removed by simple a high-yielding reaction with trifluoroacetic acid[110] or hydrochloric acid.[111,112]

1.11.4 Production of 45.

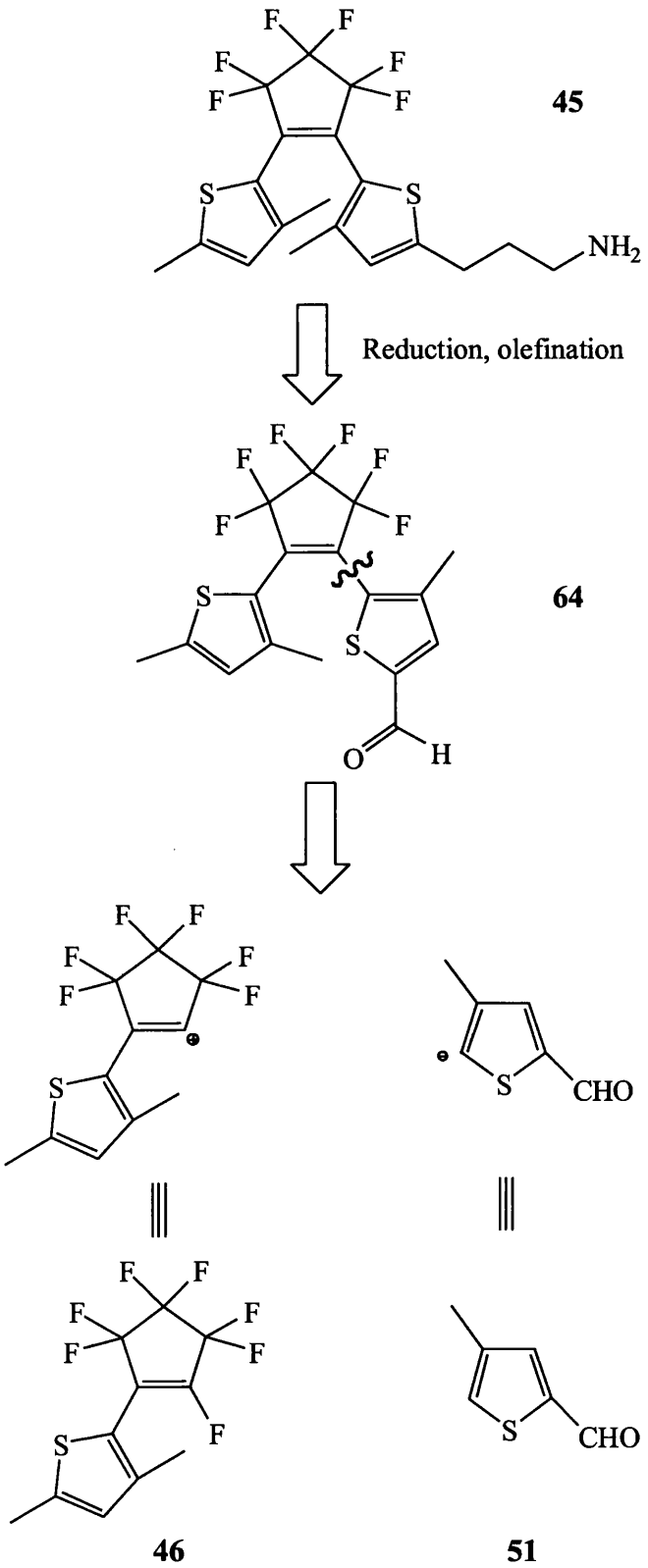
If the use of one of the protected groups described in Section 1.11.3 allows the production of a protected derivative of the target molecule **45** as shown in **Scheme 1.30**, it should be a simple matter to remove the protecting group from the amine to yield **45**, as shown in **Scheme 1.35** (using generic protected amine **59** as an example).



Scheme 1.35: Proposed deprotection of protected amine 59 (cf. Scheme 1.31), probably in acidic conditions (cf. Section 1.10.3), to produce 45.

As the spectroscopic properties are very important to the viability of **45** as a switchable RET acceptor for **1** it would be necessary to measure its UV-Vis spectra and photochromic performance and compare it to **21**/**22**[50] to ensure that the addition of the linkable group does not adversely affect the performance.[41]

1.12 Disconnection of 45: Protected aldehyde.

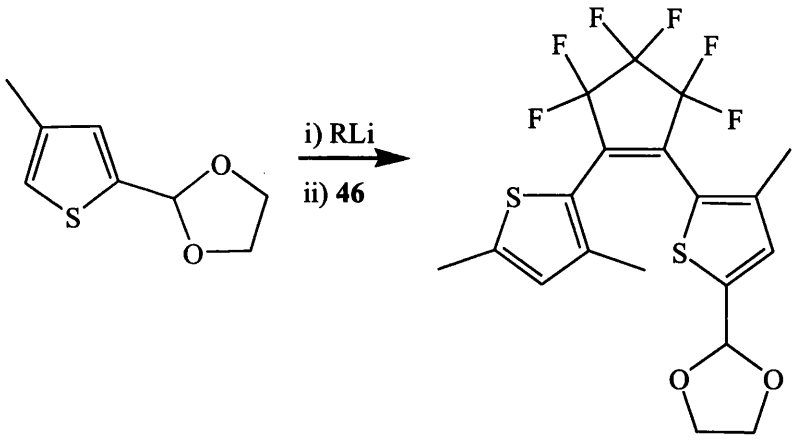


Scheme 1.36: Disconnection of 45 to give the photochromic aldehyde 64 (cf. Section 1.10.2) and then disconnection of 64 to give the two starting materials 46 and 51.

A second possible disconnection of **45** is shown in **Scheme 1.36.**

The photochromic aldehyde **64**, which has not been reported in the literature, could be converted to **45** using olefination and subsequent reduction as outlined in Section 1.11.2 for the analogous conversion of **51** to **47**.

The lithiation of **51** and subsequent reaction with **46** to form **64** would suffer from the same problem as that of the thienylpropylamine **47**; the carbonyl functionality of the aldehyde would interfere with the lithiation reaction. Therefore for this reaction to work it would be necessary to protect the carbonyl group of **51,** possibly as the cyclic acetal **65,** and to react the protected aldehyde with **46** to form the photochromic acetal **66,** as shown in **Scheme 1.37**.

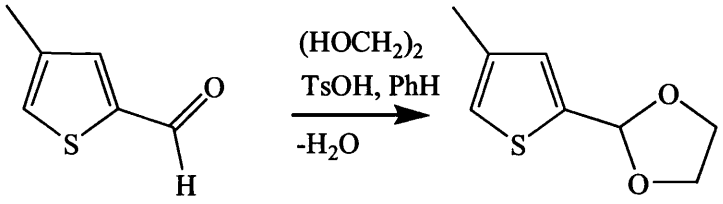


65 **66**

Scheme 1.37: Proposed lithiation of cyclic acetal 65 (a protected form of aldehyde 51) and reaction with with 46 to give the photochromic acetal 66 (cf. Scheme 1.8).

The aldehyde **51** should be easily protected as the cyclic acetal **65** by reaction with ethylene glycol in benzene in the presence of *para*-toluenesulfonic acid (TsOH). This reaction is shown in **Scheme 1.38**. This is, again, entirely dependant on being able to 5-substitute 3-methylthiophene regioselectively. This specific protection reaction has not been reported, but this type of reaction is common both in general[115] and for very similar substrates.[116] Cyclic acetals can be converted back to the aldehydes by simple reaction with hydrochloric acid in THF.[115,116,117]

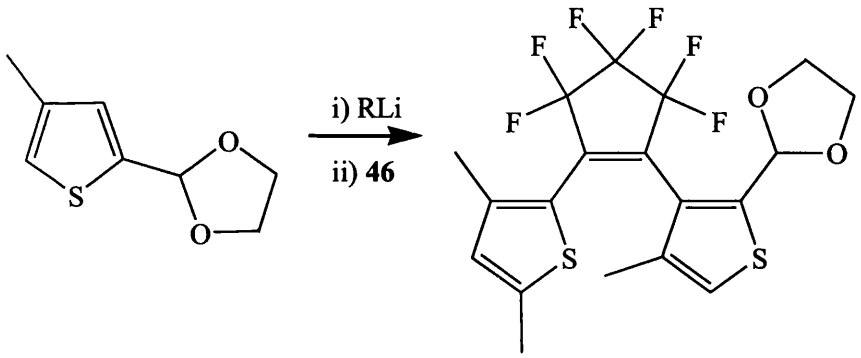
The reaction in **Scheme 1.37** appears to be viable. Cyclic acetals are known to be stable in the presence of alkyllithium reagents during substitution reactions[118] and halogen-lithium exchange reactions,[31] so the protecting group was considered a viable option.



51 65

Scheme 1.38: Proposed protection of aldehyde 51 by reaction with ethylene glycol to give the cyclic acetal 65.

A potential problem with this plan is the possible action of the acetal as a directing group for the lithiation step. It is possible that the oxygen atoms in the acetal group could fulfil a similar function to the sulfur heteroatom in the thiophene ring and direct lithiation to the 3-position of **65** to give the photochromic acetal **67**, as shown in **Scheme 1.39**.

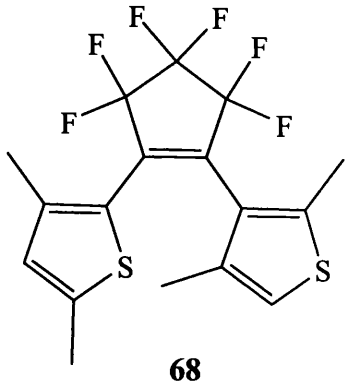


65 67

Scheme 1.39: Undesirable possible reaction of 65 with 46 (cf. Scheme 1.37) involving lithiation of 65 in the 3-position of the thiophene ring and reaction with 46 to give the unwanted product 67.

The molecule **67** contains two thiophene groups that are arranged in the same way as in molecule **68** (**Figure 1.14**), which was reported by Uchida and Irie in the same paper in which they reported molecule **21**.[50]

Molecule **68** was reported to have an open form λ_{max} of 312 nm ($\varepsilon = 1.2 \times 10^4$ $dm^3mol^{-1}cm^{-1}$ $\Phi_{A\rightarrow B} = 0.28$) and a closed form λ_{max} of 469 nm ($\varepsilon = 4.5 \times 10^3$ $dm^3mol^{-1}cm^{-1}$ $\Phi_{B\rightarrow A} = 0.57$) in hexane. These are different from the values given for **21** (open form λ_{max} of 336 nm ($\varepsilon = 1.3 \times 10^4$ $dm^3mol^{-1}cm^{-1}$ $\Phi_{A\rightarrow B} = 0.40$), closed form λ_{max} of 425 nm ($\varepsilon = 5.8 \times 10^3$ $dm^3mol^{-1}cm^{-1}$ $\Phi_{B\rightarrow A} = 0.58$) in hexane.



68

Figure 1.14: The unsymmetrical photochromic diarylperfluorocyclopentene 68 as reported by Uchida and Irie in 1995,[50] which is a regioisomer of and has different UV-Vis Spectral characteristics to 21 (cf. Figure 1.10), and is analogous in structure to molecule 67 (cf. Scheme 1.39).

The cyclic acetal group was not expected to greatly affect the photochemical properties of the molecules as it would not extend the conjugation, so it was thought that the UV characteristics could be used to tell the two possible isomers, **66** and **67** apart. Other techniques such as NMR spectroscopy and X-ray diffraction could also be used to confirm the structure of the product of the reaction shown in **Scheme 1.37**.

1.13 Conclusion to the introduction.

Utilising criteria obtained from the Förster theory of energy transfer (Section 1.3), molecule **21** (**Figure 1.9**, Section 1.6), was selected as a molecule that could conceivably operate as a photoswitchable energy transfer acceptor for the fluorescent molecule *N*-methylacridone (**1**, Section 1.1). Its photoswitched form (molecule **22,** cf. **Scheme 1.10**) absorbs light at the emission wavelength of **1** but molecule **21** itself does not.

It was necessary to synthesise the molecule **21** in order to evaluate its viability as a photoswitchable acceptor for **1**, which could be done by measuring the spectral overlap integral, $J(\lambda)$, of the emission spectrum of **1** and the absorption spectrum of **22**, and using that measurement to calculate the Förster distance R_0 of the proposed donor-acceptor pair (Section 1.3.2) and comparing that with the proposed linking strategy (Section 1.3.3). If R_0 is larger than the length of the proposed linker chain, 11.3 Å, then RET can be assumed to occur.

In order to synthesise **21** a convenient and selective method of synthesising 2,4-dimethylthiophene (**23**), preferably *via* selective lithiation and substitution of 3-methylthiophene (**38**) was needed (Section 1.6.4).

The molecule **45** was designed to fulfil the criteria of having an amino functionality for linking while retaining the spectral characteristics of molecule **21** (Section 1.10).

Several possible plans for the synthesis of **45** have been outlined, and analogous examples taken from the literature have been used to evaluate the potential for success of those methods (Sections 1.11, 1.12). All of these methods depend on finding a regioselective general method for 5-substitution of **38**, as all of the methods involve 2-substituted-4-methylthiophenes as starting materials.

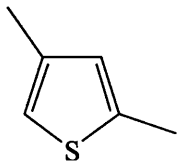
The rest of this thesis will deal with how these plans were carried out.

Chapter Two:

Development of a method for the highly selective 5-substitution of 3-methylthiophene

2.1. Introduction.

As has previously been described in Section 1.6 the first stage in this project, the synthesis of the photochromic molecule **21** (cf. **Figure 1.9**), was complicated by the lack of availability of the starting material 2,4-dimethylthiophene (**23**, **Figure 2.1**). There was therefore a need to synthesise **23** in high yield as a starting material.



23

Figure 2.1: 2,4-dimethylthiophene (23).

There are several methods of synthesis of **23** in the literature, but all are flawed in some way. For example, starting materials that are not commercially available or very expensive are needed, prohibitively harsh reaction conditions are required or low yields of product are reported (cf. Section 1.8).[59-64]

Most methods for the synthesis of **23** found in the literature, regardless of other failings, were specific to **23** and might have been difficult to adapt in order to make the other starting materials that would be needed for the later stages of this project (cf. Sections 1.11, 1.12). The only method that seemed applicable to the task was the lithiation of 3-methylthiophene (**38**) and subsequent reaction with an electrophile which, although not highly selective, was reported as high-yielding and had in the past been adapted to increase the selectivity (cf. Sections 1.8.3 & 1.9.2).[65,68,77,78]

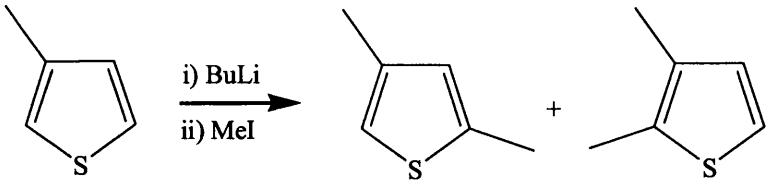
The research described in this chapter was directed towards enhancing the selectivity of lithiation of **38** and, by varying the electrophile used in the subsequent reaction, to develop a general method for the highly regioselective 5-substitution of **38**.

2.2. Initial lithiation of 38 with *n*-butyllithium.

2.2.1. Lithiation reaction.

The first experiment that was carried out was a simple lithiation of **38** with *n*-butyllithium and subsequent reaction with iodomethane (MeI). The reaction was carried out under an argon atmosphere for 1 hour at room temperature. MeI was added neat and the reaction was stirred at room temperature for a further two hours.

This reaction was conducted for purposes of comparison with reports in the literature which suggested that the reaction would produce a mixture of 2-substituted and 5-substituted **38**. Were this the case this reaction would produce the products 2,3-dimethylthiophene (**44**) and **23** respectively. This reaction is shown in **Scheme 2.1**.



38 **23** **44**

Scheme 2.1: The predicted results of lithiation of 38 with BuLi and subsequent reaction with MeI. The products 23 and 44 would be expected with 23 predominating due to steric factors

It was expected that the 5-substituted product, **23**, would predominate due to the slight reduction of steric hindrance of the 5-position of **38** in comparison with the 2-position. No 4-substitution (β-substitution) was expected to occur due to the α-directing effect of the sulfur atom.

2.2.2. Results and discussion.

The lithiation reaction did indeed give two products. The GC trace of the reaction mixture after aqueous workup using diethyl ether (Et_2O) as the extraction solvent and drying over anhydrous magnesium sulfate is shown in **Figure 2.2.**

There were two resolved peaks that had very similar retention times. The area of the earlier, larger peak was 3.5 times that of the later peak. If the reaction had proceeded as expected then the earlier peak would correspond to **23** and the later peak to **44**. There was

no evidence of starting material (**38**) and product upon evaporation of the reaction mixture corresponded to a quantitative yield of dimethylthiophene.

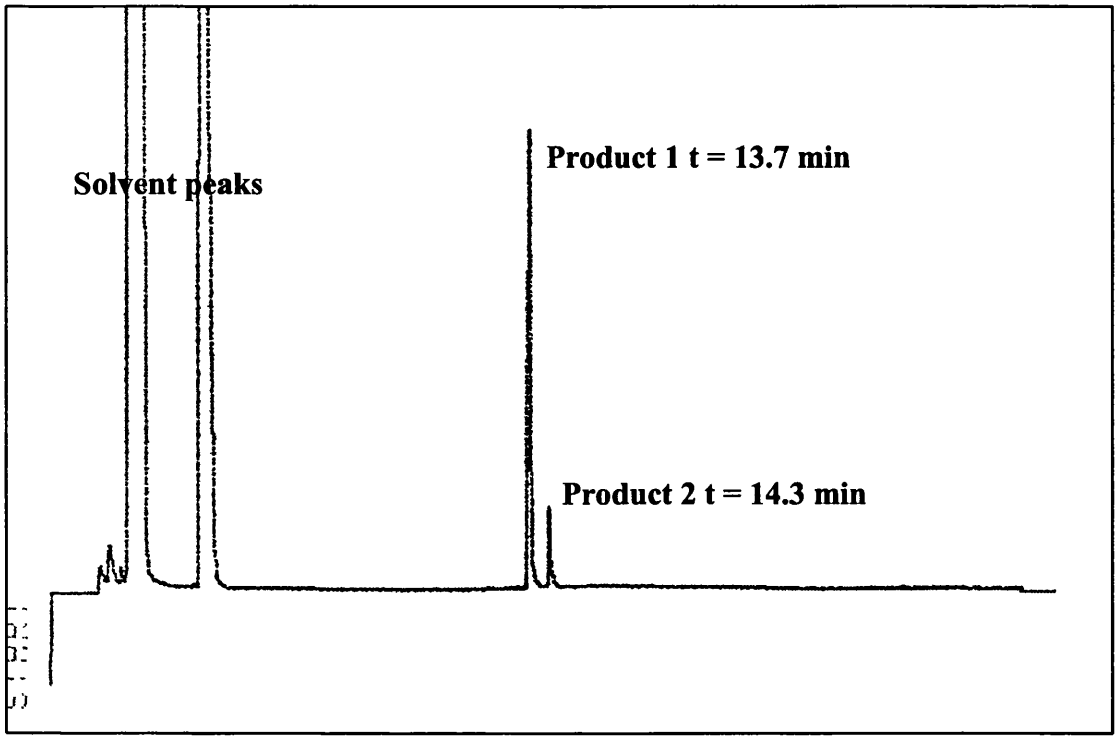


Figure 2.2: The Gas Chromatographic (GC) trace of the lithiation reaction shown in Scheme 2.1 The trace shows two solvent peaks (corresponding to Et_2O and THF) and two product peaks; product 1 (t = 13.7 min) and product 2 (t = 14.3 min), with an area ratio of approximately 3.5:1.
GC conditions are given in the experimental section.

The products were identified from the ^1H NMR spectrum of the reaction mixture after purification by distillation under atmospheric pressure. The products both distilled over at a temperature of 139 °C, which corresponds to the reported boiling point of both of the dimethylthiophene isomers that were expected to be produced by this reaction.[65]

The ^1H NMR spectrum of the product mixture is shown in **Figure 2.3.**

The NMR spectrum supported the GC results, in that it showed a mixture of two isomeric compounds. The two signals in the aliphatic hydrocarbon region of equal integration signified the presence of two methyl groups in each isomer and the ratio between the major and minor components was approximately 3.5, which correlated with the GC analysis. The crucial structural elucidation was based on the aromatic signals between δ = 6.45 and 6.90 ppm. An enhanced view of this region is shown in **Figure 2.4.**

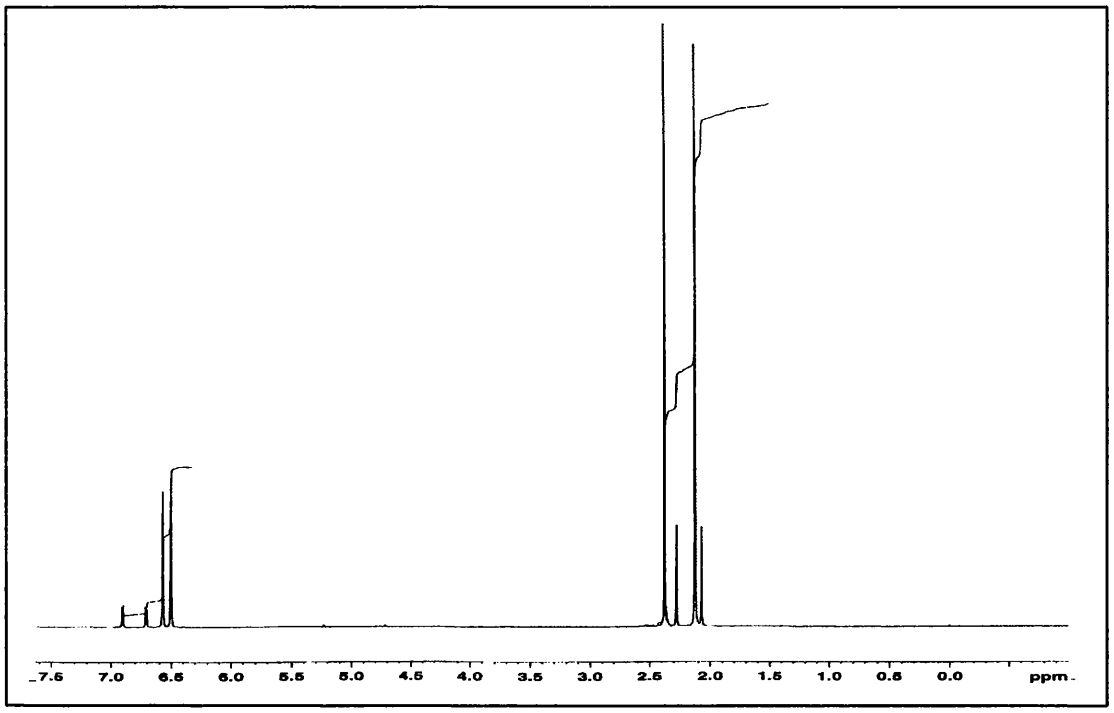


Figure 2.3: ^{1}H NMR spectrum of the initial lithiation reaction (cf. Scheme 2.1 and Figure 2.2). The spectrum was of the product of the reaction after distillation and was measured in $CDCl_3$.

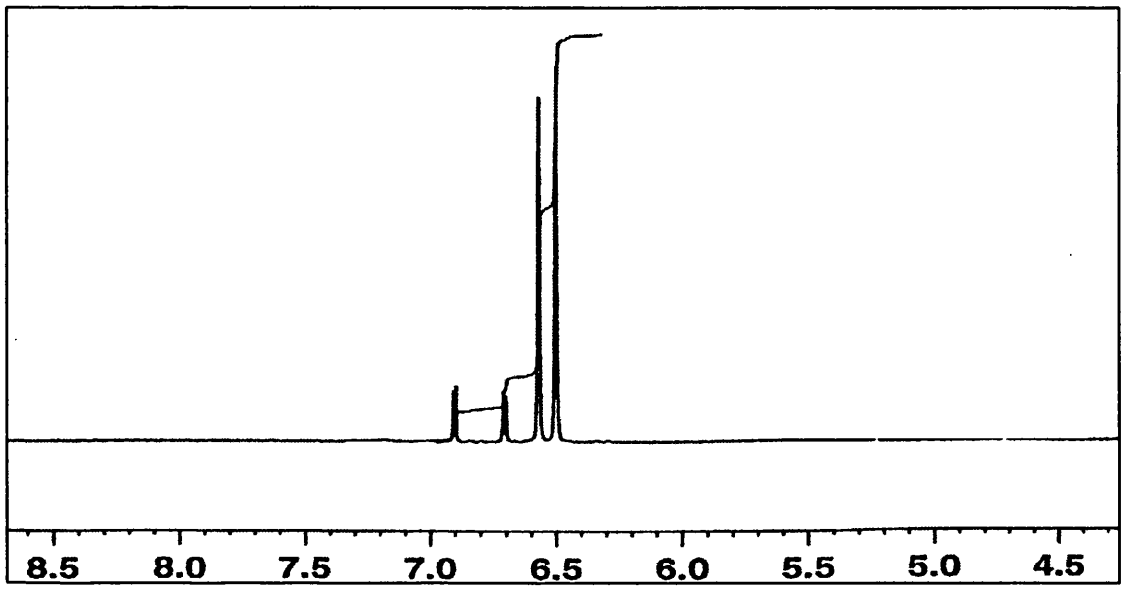
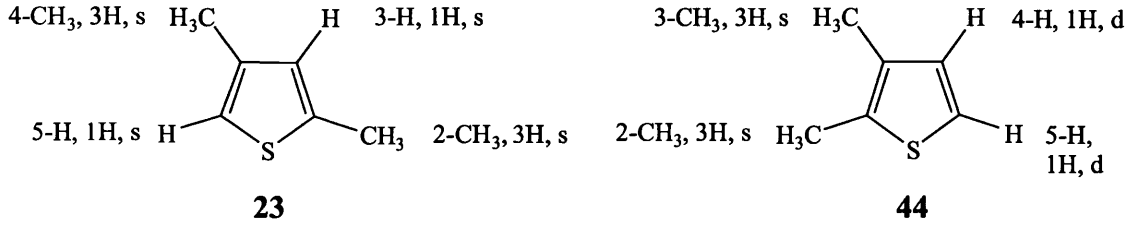


Figure 2.4: An enhanced view of the aromatic region of the ^{1}H NMR spectrum of the products of the initial lithiation reaction, the full spectrum of which is shown in Figure 2.3. The two singlets correspond to the major product 23, and the doublets to the minor product 44.

This pattern in the NMR spectrum corresponds exactly with what would be expected if the major product was **23**, which would have two singlets in the aromatic region signifying its uncoupled ring hydrogens and the minor product was **44**, which would have two doublets due to the coupling of the adjacent ring hydrogens. More detailed ^{1}H NMR spectral expectations are shown in **Figure 2.5.**[119]



23 **44**

Figure 2.5: ^{1}H NMR expectations for 23 and 44. The numbering system for thiophenes is explained in Figure 1.13. All the methyl peaks are predicted to be singlets (s) due to the lack of neighbouring hydrogens. The ring hydrogens of 23 (3-H and 5-H) should also be singlets as they, again, have no neighbouring hydrogens with which to couple. The ring hydrogens in 44 (4-H and 5-H), however, are in adjacent positions on the ring and should couple with each other, leading to doublets (d) in the ^{1}H NMR spectrum. This can be seen in Figure 2.3.

Mass Spectrometry (EI^+)[120] showed a pseudo-molecular ion peak at m/z = 111, which corresponds to the $[M-H]^+$ ion of dimethylthiophene. From this evidence it was concluded that the products were **23** and **44** with **23** predominating as was expected.

Although high-yielding, the reaction was not highly selective, but the preferentially formed product was the desired product **23**. The closeness of the two peaks in the GC trace and futile attempts to separate the isomers by TLC led to the conclusion that, while the isomers were separable analytically it would be impractical to attempt to separate them preparatively. The only way the reaction could therefore be made to work sufficiently well would be to increase the selectivity of the reaction in favour of the already preferentially-formed product.

2.3. Temperature variation of lithiation of 38 with *n*-butyllithium.

2.3.1. Variation of reaction temperature.

As a first attempt at modifying the reaction, the temperature of reaction was varied while keeping all other conditions, such as reaction time, the same. It was hoped that by lowering the temperature of reaction, the lithiating reagent would be less likely to lithiate in the more sterically hindered position and the selectivity of the reaction would therefore increase.

2.3.2. Results and discussion.

The results of the temperature experiment are shown in **Table 2.1.** The area ratio between the isomers in the GC trace of the reaction mixture is used to describe the selectivity of the reaction.

	Temperature °C	**23:44**[c]	Combined % Yield (GC)[d]
1	RT	3.5:1	99
2	0[a]	4:1	90
3	-78[b]	4.4:1	56

Table 2.1: Results of temperature variation in the lithiation of 38 with *n*-butyllithium (cf. Scheme 2.1). Lithiation was carried out for 1 hour and the reaction was stirred with MeI for a further 2 hours (see Section 2.9.4 for experimental details).

a. Temperature of 0 °C was obtained using an ice/water bath.
b. Temperature of -78 °C was obtained using a dry ice/acetone bath.
c. Calculated by the area ratio of the product peaks in the GC trace.
d. For details of GC yield calculations see the experimental section.

It can be seen from the results in **Table 2.1** that the selectivity of the reaction did indeed increase as temperature was lowered, although the actual increase in selectivity was not very large, and certainly not enough to be synthetically useful. The yield of reaction was lowered at 0 °C and considerably so at -78 °C (the remainder of starting material was recovered to give a mass balance of roughly 100% for both reactions). This was attributed to the reduction of reaction temperature increasing the reaction time, and thus decreasing the yield in the time allotted for the reaction. It was decided that decreasing the reaction temperature was not a promising enough course of action.

2.4. Variation of lithiation reagent.

2.4.1. Variation of lithiation reagent.

The directing effect of bulky 3-substituents and of bulky electrophiles towards increased 5-selectivity in the lithiation reactions of 3-substituted thiophenes is evident in the literature and was discussed in Section 1.9.2.

This presented the most promising idea for a method of increasing selectivity of substitution, but neither effect could be utilised in improving the reaction in question, as the 3-substituent of the substrate **38** is a methyl group and the electrophile is also a methyl group, both of which are not highly sterically hindered. The only sterically variable constituent of the reaction was the lithiating reagent used in the first step. As was also discussed in Section 1.9.2, increasing the bulkiness of the lithiating reagent has also been reported to increase the 5-selectivity of this type of reaction.

In light of this, it was decided to use lithiating reagents of varying steric hindrance in order to direct lithiation to the 5-position.

2.4.2. Results and discussion.

The results of the variation of lithiating reagents are shown in **Table 2.2.** Methyllithium was used simply as a comparison although it was predicted that the selectivity of that reaction would be less even than that of *n*-butyllithium. Various organolithium reagents were used as bought. Lithium amides were generated *in situ* by the reaction of the corresponding secondary amines with *tert*-butyllithium at -78 °C.

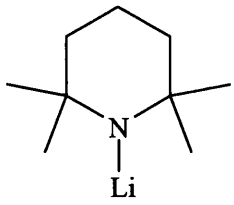
As can be seen from the results in **Table 2.2**, the selectivity of the reaction generally increased with increased steric hindrance of the lithiating reagents. Some lithium amides, as they are weaker bases than the lithium alkyls and would therefore take longer to react, gave low yields of product (mass balances for thiophenes were all around 100%) as does *n*-butyllithium, but the trend of increased selectivity is still demonstrated by these results.

	Organolithium reagent	**23**:**44** ratio[a]	Combined % Yield (GC)[b]
1	methyllithium	3:1	87
2	*n*-butyllithium	4.4:1	56
3	*tert*-butyllithium	5:1	91
4	*tert*-butyllithium/TMEDA	7:1	96
5	lithium di-*iso*-butylamide	9:1	40
6	lithium piperidide	10:1	42
7	lithium dicyclohexylamide	15:1	48
8	lithium di-*sec*-butylamide	16:1	95
9	lithium 2,2,6,6-tetramethylpiperidide	79:1	97

Table 2.2: Use of different lithiating reagents in the reaction of 38 with MeI and the resulting change in reaction selectivity. Lithiation was carried out at -78 °C for 1 hour for maximum selectivity, MeI was added and the mixture was stirred for a further 2 hours while warming to room temperature (see Sections 2.9.4 & 2.9.5 for experimental details).

a. **Calculated by the area ratio of the product peaks in the GC trace.**
b. **For details of GC yield calculations see the experimental section.**

The most dramatic increase came with the use of lithium 2,2,6,6-tetramethylpiperidide (LiTMP, **69**, **Figure 2.6**), which is a highly hindered and highly rigid molecule and is also a stronger base than most other lithium dialkylamides.[121]



69

Figure 2.6: Lithium 2,2,6,6-tetramethylpiperidide (69) a strong, hindered and rigid organolithium reagent that can greatly increase the selectivity of a lithiation reaction.[121]

Lithiation of **38** with LiTMP followed by treatment with iodomethane gave essentially pure **23** in high yield in a convenient one-pot procedure. The GC trace of the reaction product is shown in **Figure 2.7** (cf. **Figure 2.2**).

It can be seen from **Figure 2.7** that the lithiation of **38** with **69** produces **23** with only a small amount of **44** as an impurity. The reaction mixture is clean, with all of the starting material **38** being consumed and any excess iodomethane evaporating off easily and the yield of product is over 95 % as calculated by GC analysis. The amine, 2,2,6,6-tetramethylpiperidine (HTMP), which is regenerated during the workup, can be removed in the form of the hydrochloride salt by washing with 2M aqueous HCl, can be recovered in high yield by treating the aqueous phase with 2M aqueous sodium hydroxide and extracting with diethyl ether, and can be re-used.

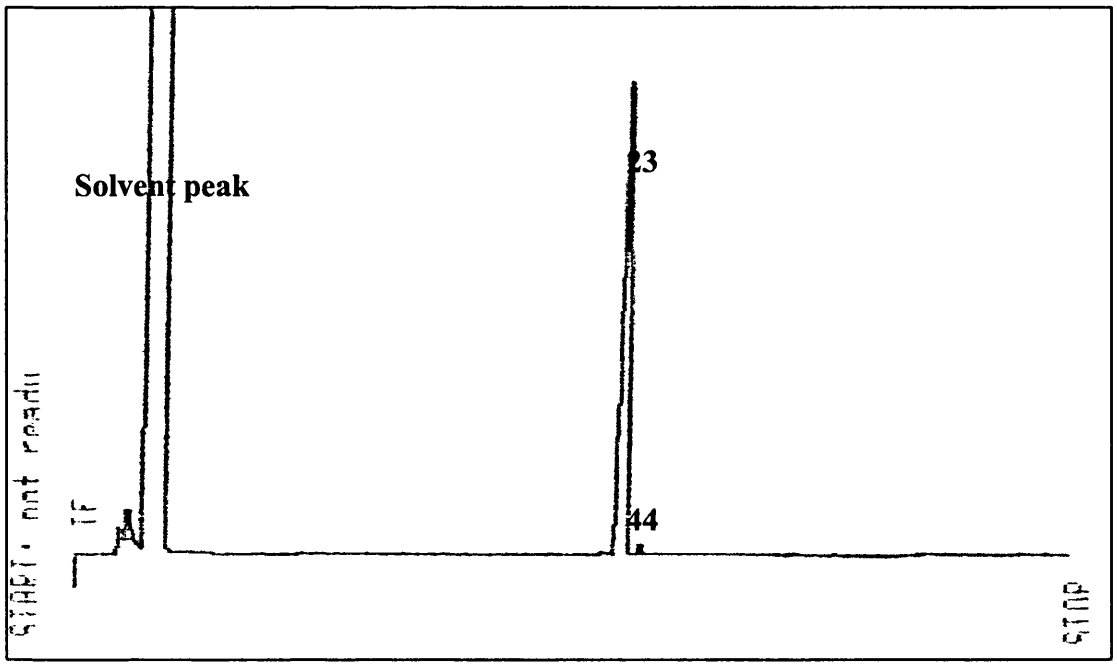


Figure 2.7: GC trace of the reaction product following the selective lithiation of 38 with 69 and subsequent reaction with MeI (cf. Figure 2.2). GC conditions are given in the experimental section.

The NMR spectrum of the product **23**, obtained as described above, is shown in **Figure 2.8** (cf. **Figure 2.3**) and a blow-up of the aromatic region is shown in **Figure 2.9** (cf. **Figure 2.4**). It can again be seen from the almost total absence of the doublets in the aromatic region that were present in **Figures 2.3** and **2.4** that the by-product **44** had been almost totally eliminated from the product mixture. ^{13}C NMR analysis correlated well with predictions. The crude product was distilled under reduced pressure to give a product that was 97.2 % pure by GC. This sample was used to calculate the yield of the reaction by internal standard GC analysis, and the yield was measured to be 98% (details of internal standard GC analysis are given in the experimental section). High-resolution MS (EI) showed an ion at m/z = 111.0262, which correlated with the calculated mass for the

deprotonated form of **23**, which was 111.0263. More detailed characterisation data is given in the experimental section.

In conclusion, it is now possible to synthesise **23** conveniently and in high yield using the simple one-pot lithiation of **38** with **69** and reaction with MeI.

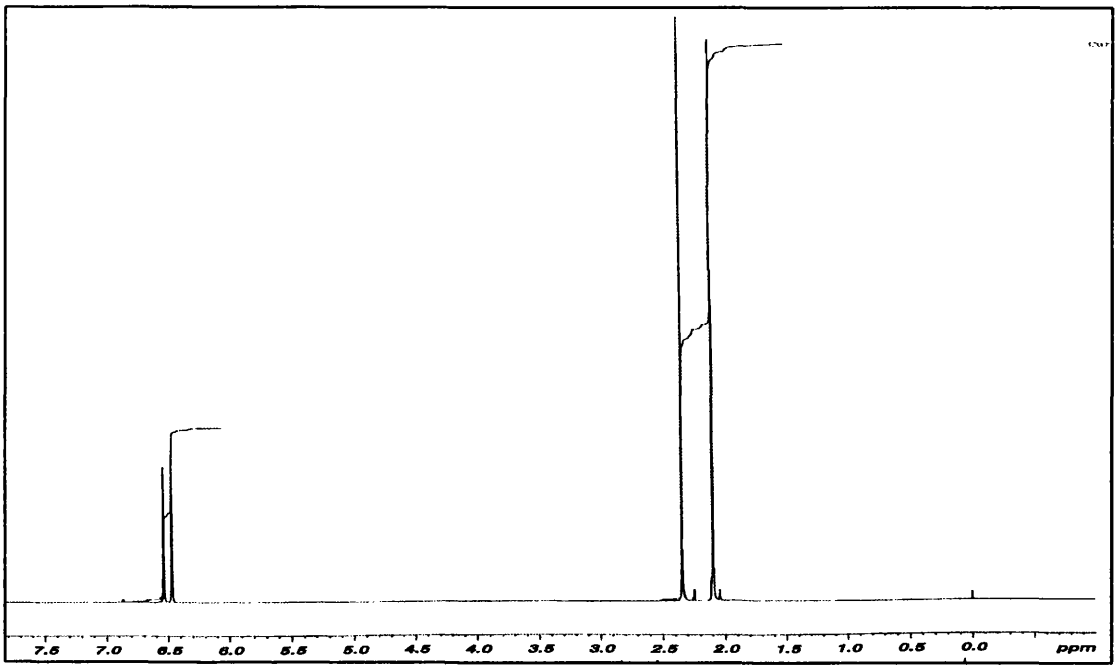


Figure 2.8: ^{1}H NMR spectrum of 23 as produced by the lithiation of 38 with 69 and treatment with MeI (cf. Figure 2.3)

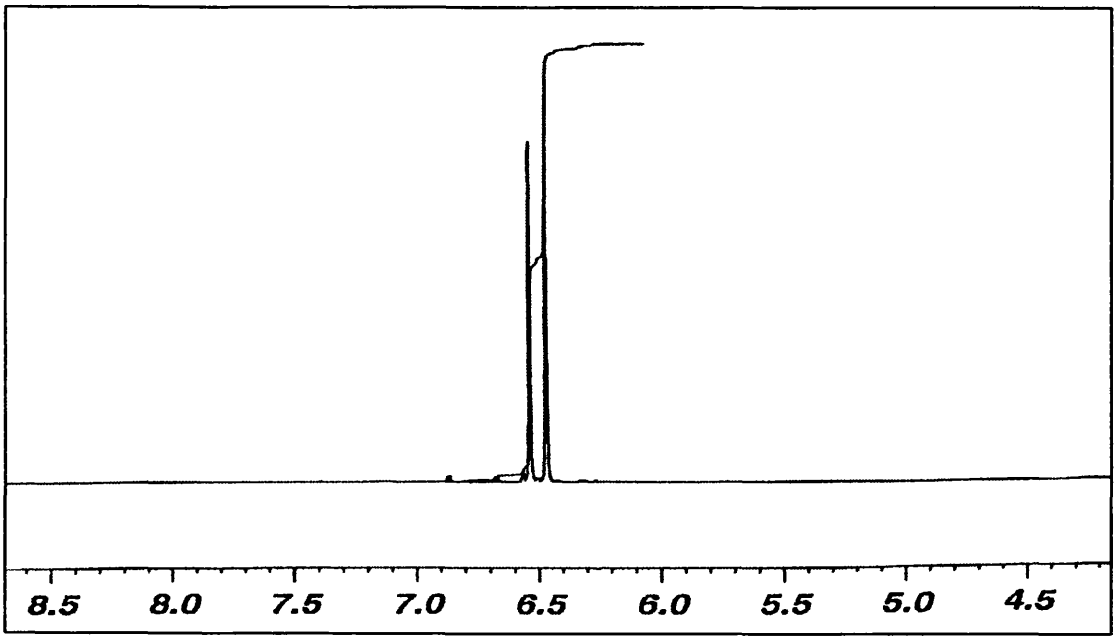
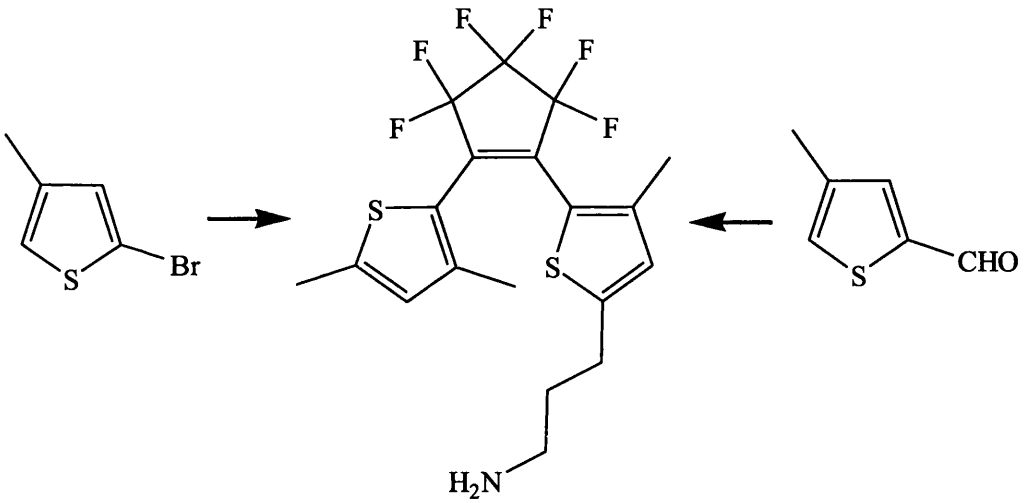


Figure 2.9: A blow-up of the aromatic region of the ^{1}H NMR spectrum of 23 as shown in Figure 2.8 (cf. Figure 2.4). It can be seen that the doublets that signify the presence of the unwanted by-product 44 are almost totally absent.

2.5 Synthesis of essential starting materials for the synthesis of 45.

2.5.1 Introduction.

As stated in Chapter 1, aside from the need for **23** itself, one of the chief reasons for development of this selective substitution method was the need for other 2-substituted-4-methylthiophenes to use as starting materials for the synthesis of the target molecule **45**. Specifically, the starting materials shown in **Figure 2.10**, 2-bromo-4-methylthiophene (**48**, Section 1.11.1) and 4-methyl-2-thiophenecarboxaldehyde (**51**, Sections 1.11.2 and 1.12) would be needed if any of the planned syntheses of **45** were to be successful.



48 **45** **51**

Figure 2.10: Compound 45, the proposed linkable photochromic acceptor molecule and 48 & 51, the two possible starting materials for the synthesis of 45 (cf. Schemes 1.24, 1.25 and 1.36).

Both **48**[79] and **51**[65,55c] have been reported before in the literature. The synthesis of **48** was reportedly achieved *via* lithiation of **38** and reaction with carbon tetrabromide (CBr_4), and was reported to favour the 2,4-disubstituted product and to give a high yield. The synthesis of **51** was reportedly achieved *via* lithiation of **38** and reaction with *N*,*N*-dimethylformamide (DMF) and was shown to have suffered from a non-selective lithiation step, as was the reported synthesis of **23**.

It was therefore necessary to demonstrate the applicability of the LiTMP lithiation of **38** to a variety of electrophiles other than MeI in order to synthesise **48** and **51**, and also to create a library of selectively-substituted compounds to attest to the generality of this method. To this end several different electrophiles including CBr_4 (and other brominating agents), DMF and others were used in the place of iodomethane.

2.5.2 Synthesis of 48.

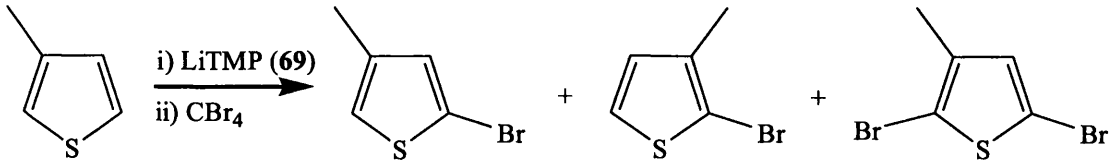
As one of the planned syntheses of **45** involved a palladium-catalysed Heck coupling of **48** with acrylonitrile (**49**, cf. **Scheme 1.24**) it was desirable to synthesise **48**. The previous report of the synthesis of **48** by Consiglio *et al.* in 1982[79] mentioned that the lithiating reagent used, *n*-BuLi/TMEDA, gave a selectivity of 13.3:1 in favour of **48** over the by-product, 2-bromo-3-methylthiophene (**70**). It is also mentioned that CBr_4 can successfully brominate more than one mole equivalent of lithiated substrate, so 0.67 mole equivalents of CBr_4 in relation to **38** were used. The yield of the reaction was reported to be 68 %. It was hoped that the selectivity of this reaction could be enhanced through the use of **69** as the lithiating reagent without affecting the yield.

Compound **38** was lithiated with **69** in dry THF at -78 °C. After one hour CBr_4 (0.67 mole equivalents) in solution in THF was added slowly and the mixture was stirred overnight. After acidic workup to remove the HTMP the mixture was analysed by GC (conditions are given in the experimental section). It was found that there was a small amount of the starting material **38** present at t = 5.8 minutes, two very closely-eluting peaks with an area ratio of approximately 13:1 at t = 15.1 and 15.30 minutes and a large peak at t = 19.3 minutes.

Tandem Gas Chromatography/Mass Spectrometry (GC-MS) analysis showed that the peaks at t = 13.1 and 15.1 each gave two isotope peaks with equal intensities at *m/z* = 176 and 178, which is what would be expected for the molecular ion of the expected isomeric monobrominated products and a single peak at *m/z* = 97 which corresponds to loss of a bromine atom from **48**. This was a very strong suggestion that these peaks were the expected products. The crude NMR spectrum was difficult to interpret due to the presence of **38** and the other product but the presence of singlets in the aromatic region which were much larger than the doublets also evident suggested that **48** was the predominant isomer (cf. **Figure 2.5**). If the major product was **48** then the ratio of **48**:**70** was 13:1, which is very similar to that reported by Consiglio.

GC-MS analysis of the peak at t = 19.3 minutes showed a pattern of three peaks in an approximately 1:2:1 ratio at *m/z* = 254, 256 and 258, which is what would be expected if **48** had been brominated further to form a dibromo product.

From this evidence, the desired monobromination of **38** to **48** had occurred and almost all of the starting material **38** had been consumed in the reaction, but the reaction had not halted with monobromination and a significant amount of dibromination had occurred giving a roughly 2:1 mixture (calculated from the measured areas of the GC peaks) of mono- and dibrominated products. The reaction is shown in **Scheme 2.2**. The occurrence of further bromination made any certain determination of the selectivity of monobromination impossible. The structure of the dibrominated product **71** was not rigorously confirmed, but is likely due to the preference of thiophenes for reaction at the α-position and indication in the literature that this is the preferred dibromination product of **38**.[80a]



38 **48** **70** **71**

Scheme 2.2: The results of the lithiation of 38 with LiTMP and reaction with CBr_4. GC and GC-MS analysis suggests that both the isomers 48 and 70 are present, as well as the dibromo product 71.

The apparent poor selectivity of the reaction in comparison to the analogous reaction with iodomethane was thought to have resulted from the susceptibility of **38** to electrophilic bromination in the 2-position which has been reported in the literature.[68,80] It was possible that the lithiation of **38** with **69** and subsequent bromination was as selective as in the methylation reaction, but proceeding alongside that reaction was an electrophilic bromination at the 2-position of **38** producing the product **70**. This would serve to decrease the selectivity of the production of **48** that would be observed in the reaction mixture. The dibromination reaction could also favour one particular monobrominated isomer over the other, further affecting the apparent selectivity.

The bromination reaction was briefly investigated with the aim of optimising the selectivity and reducing the amount of dibromination. The amount of CBr_4 was varied

while keeping all other reaction conditions the same. The results of these experiments are shown in **Table 2.3**.

	Mole equivalents of CBr_4 used[a]	% of **38** consumed.[b]	Ratio of **48**:**70** [c]	% of **71** in the reaction mixture.[c]
1	0.66	93.3	13.0:1	28.4
2	0.5	58.6	12.5:1	25.5
3	0.25	29.1	13.6:1	0

Table 2.3: Results of varying the amount of CBr_4 in the lithiation-bromination of 38 with 69 according to Scheme 2.2.

a. **Compound 38 was stirred with 69 in THF at -78 °C for 1 hour, CBr_4 was added in THF and the mixture was stirred overnight (see Section 2.9.7 for experimental details).**
b. **Measured by internal standard GC analysis, see experimental for details. N.B. % values calculated simply from relative peak areas of reagent and products in the GC trace correlated with the values calculated by internal standard analysis.**
c. **Calculated from the peak areas in the GC trace.**

It can be seen from **Table 2.3** that when the amount of CBr_4 was reduced to 0.5 mole equivalents the consumption of **38** was reduced considerably while there was little change in the selectivity of production of **48** or the amount of dibromination. However, when 0.25 equivalents of CBr_4 were used it appeared that, although only 29 % of **38** had been consumed, no dibromination had occurred. There was still no improvement in the selectivity of the reaction. It was considered prudent to try to find a method that would not suffer from overbromination but would consume more of the starting material.

It was decided to attempt to use other brominating reagents as electrophiles in order to gauge the effect that this would have on the selectivity of the reaction and the overbromination. 1,2-Dibromoethane,[79,122] elemental bromine (Br_2) and *N*-bromosuccinimide (NBS) were used in the place of CBr_4. The results are shown in **Table 2.4.**

It can be seen from the results in **Table 2.4** that there did not appear to be any dibrominated product formed when any of the other electrophiles, even elemental bromine, were used. The dibromination appeared to be confined to when CBr_4 was used.

	Brominating agent.[a]	% of **38** consumed[b]	**48**:**70**[c]	% of **71** in the reaction mixture[c]
1	CBr_4 (0.66 mol. eq.)	93.3	13.0:1	28.4
2	1,2-Dibromoethane	14.8	2.7:1	0
3	Br_2	70.2	3.5:1	0
4	NBS	46.1	12.5:1	0

Table 2.4: Results of varying the brominating agent in the lithiation of 38 with 69 and subsequent bromination to give the bromomethylthiophene isomers 48 and 70 and the dibromomethylthiophene product 71.

a. **Compound 38 was stirred with 69 in THF at -78 °C for 1 hour, brominating agent (1 mol. eq. unless indicated) was added in THF and the mixture was stirred overnight (see Section 2.9.7 for experimental details).**
b. **Measured by internal standard GC analysis, see experimental for details.**
c. **Calculated from the peak areas in the GC trace.**

The use of 1,2-dibromoethane resulted in a very low starting material consumption and a very low selectivity. It has been suggested in the literature that the conversion of the thienyllithium intermediate (cf. **Scheme 1.21**) to the bromomethylthiophene product *via* 'reverse' bromine-lithium exchange with 1,2-dibromomethane is an equilibrium and that the thienyllithium, being more stable, is the more favoured product of that equilibrium.[79] An alternative explanation of the low consumption could be the possible deprotonation of the 1,2-dibromoethane. Regardless of the explanation, the thienyllithium would regenerate **38** upon aqueous workup. The low selectivity could again be due to the susceptibility of **38** to bromination in the 2-position.

The use of elemental bromine resulted in a much higher starting material consumption, perhaps due to the higher activity of the reagent. The selectivity is very low, however, and this is probably also due to the higher reactivity of bromine leading to more electrophilic bromination at the 2-position of **38**.

The use of NBS as the brominating agent provided the best result. 46.1 % of **38** was consumed with no evident overbromination to give **48** with 12.5:1 selectivity over **70**. The selectivity of the reaction was similar to that reported by Consiglio but was again not comparable to the selectivity of the reaction with iodomethane reported earlier in this chapter. It was reluctantly concluded that electrophilic bromination at the 2-position of **38** to give **70** would probably always be a competing reaction and that the selectivity of production of **48** from **38** would probably never be as high as that of the production of **23**.

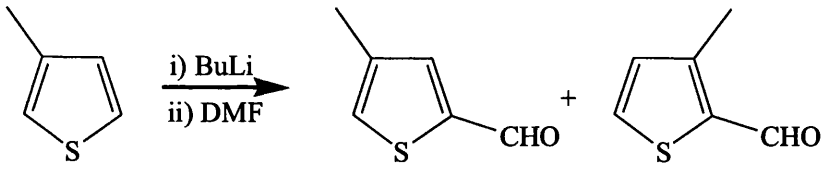
The product of the reaction with NBS was worked up to provide a sample of **48** for characterisation.

The starting material **38** has a boiling point of 112 °C and was easily removed from the reaction mixture by distillation at room temperature. The ^{1}H NMR spectrum of the residue showed a mixture of two products in a ratio of 12.7:1. The previous assumption that the major product was **48** was confirmed by the presence of two singlets ($\delta = 6.56$ and 6.68 ppm) in the aromatic region for the major product, corresponding to the uncoupled ring hydrogens of **48** (cf. **Figure 2.5**). The major product also had a methyl signal at $\delta = 2.03$ ppm). This observed data correlates with that published by Consiglio.[79] The spectrum of the minor product showed the methyl signal at $\delta = 2.01$ and two doublets at $\delta = 6.60$ and 6.96 which correspond to the coupled ring hydrogens of the minor product **70**. This correlates with published data for **70**.[80c] ^{13}C NMR data also correlated well with the literature. MS analysis of the residue showed the aforementioned 1:1 ratio of peaks at m/z = 176 and 178 and the single peak at m/z = 97 signifying loss of bromine, which correspond to what would be expected for **48**/**70**. More detailed characterisation data are given in the experimental section.

In conclusion, the method of highly selective 5-substitution of **38** *via* lithiation with **69** and subsequent reaction with an electrophile did not prove as successful for bromination as it did for methylation. Reaction with a variety of brominating agents gave poor yields of the required product **48** arising from apparent poor consumption of the starting material **38**, but the only instance of high starting material consumption observed was accompanied by a large amount of dibromination to form **71**. The selectivity of the reaction was also comparatively poor, with the best values being comparable to the work of Consiglio *et al.*, who reported a much better yield.[79] The low yield and low selectivity of this reaction meant that it would be inconvenient to use **48** as a starting material for the synthesis of **45**, although if no other option was viable it would be a possible route.

2.5.3 *Synthesis of* ***51.***

The two alternative syntheses of **45** that do not involve the Heck reaction of **48** both require 4-methyl-2-thiophenecarboxaldehyde (**51**, cf. **Figure 2.10**) as the starting material (cf. **Schemes 1.25** and **1.36**). In the light of the unsatisfactory synthesis of **48** it was considered vital to be able to synthesise **51** selectively and in high yield. As mentioned previously, the lithiation of **38** and subsequent reaction with DMF to give **51** has been reported, although the selectivity was low. In 2002, Collins *et al.*[55c] reported that lithiation of **38** with *n*-BuLi and reaction with DMF gave a 4:1 mixture of **51** and the by-product 3-methyl-2-thiophenecarboxaldehyde (**72**), as shown in **Scheme 2.3**. Collins' result is close to the result reported in this work for the methylation reaction following lithiation with *n*-BuLi (Section 2.2.1).



38 **51** **72**

Scheme 2.3: The results of the lithiation of 38 with BuLi and reaction with DMF as reported by Collins in 2002.[55c] The reaction was reported to give 51 and 72 in a ratio of 4:1 respectively.

It was hoped that replacing BuLi with **69** in this reaction would greatly improve the selectivity.

Compound **38** was lithiated with **69** in dry THF at -78 °C. After stirring for 1 hour DMF (1 mol. eq.) was added and the mixture was stirred overnight. After workup with hydrochloric acid to remove the regenerated HTMP the mixture was analysed by GC (GC conditions are reported in the experimental section). GC analysis showed that only 69 % of the starting material **38** had been consumed but unlike in the synthesis of **48** there were only two very closely-eluting product peaks with an area ratio of 31:1. This suggested that the reaction had been successful.

It was not clear why the reaction had not proceeded to completion but acting on indications from a similar reaction in the literature,[76a] the reaction was repeated using 2 mole equivalents of DMF instead of one. The GC of this reaction mixture showed that all

of the starting material **38** had been consumed and the resulting crude mixture was very clean, showing only the two previously mentioned product peaks this time in an area ratio of 35.5:1. ^{1}H NMR analysis of the crude product showed a singlet at $\delta = 9.78$ ppm corresponding to the expected aldehyde proton as well as the other expected signals. This correlated with data reported by Detty in 1995.[70] The by-product **72** was identified by the expected doublets in the aromatic region corresponding to the coupled ring hydrogens, and the measured selectivity correlated with that from the GC analysis.^{13}C NMR analysis showed a signal at $\delta = 183.0$ ppm corresponding to the expected aldehyde carbon and the spectrum correlated well with data published by Satonaka *et al.* in 1988.[123] A carbonyl peak was observed in the IR spectrum. The crude product was purified by reduced-pressure distillation and isolated in 89 % yield. The pure sample was used to calculate the yield of the reaction by internal standard GC analysis. The yield was calculated to be 100 %. High resolution MS analysis of the sample showed a peak at *m/z* = 125.0056 which correlated exactly with the calculated mass of the $[M-H]^{+}$ ion of **51**. More detailed characterisation data are given in the experimental section.

During the later stages of this work this reaction was repeated many times and gave consistently high yields and high selectivities.

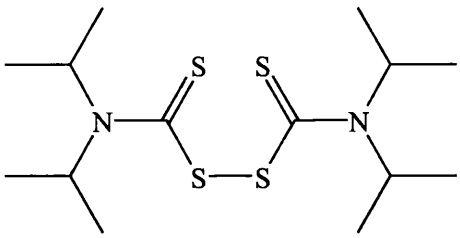
In conclusion, it is now possible to synthesise **51** conveniently and in high yield using the simple one-pot lithiation of **38** with **69** and reaction with 2 mole equivalents of DMF.

2.6 Application of the lithiation method to different electrophiles.

2.6.1 Introduction.

The successful synthesis of **51** allowed the later stages of this project to be possible, but it was considered necessary to try out this lithiation method with several more electrophiles to improve on some already published syntheses, to show that it can be legitimately described as a general method and in order to synthesise some novel compounds.

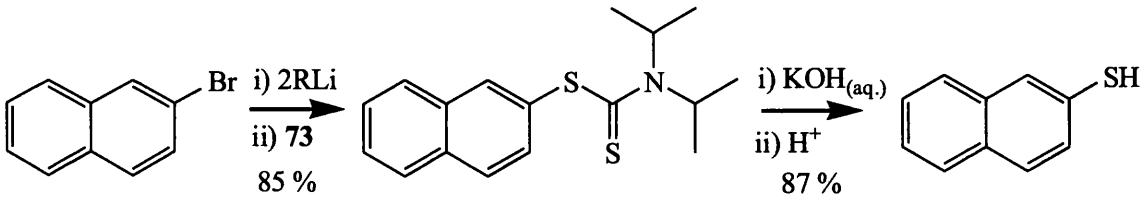
2.6.2 TITD reaction.



73

Figure 2.11: Tetra-*iso*-propylthiuramdisulfide (TITD, 73).[124] A reagent that can be used for the efficient preparation of thiols from organolithium reagents.

Tetra-*iso*-propylthiuramdisulfide (TITD, **73**, **Figure 2.11**) is a reagent that was reported by Jen *et al.* in 1982[124] to react with aryllithiums to form stable crystalline dithiocarbamates, which can be easily converted to the corresponding thiols. It has since been used several times as an electrophile in lithiation reactions.[67e-f,125] A representative reaction as reported by Jen is shown in **Scheme 2.4**. 2-Bromonaphthalene (**74**) was converted to 2-lithionaphthalene *via* bromine-lithium exchange and reacted with **73** to give the dithiocarbamate **75** in high yield, which was treated with 20 % KOH and acidified to give the thiol **76** in high yield.[124]

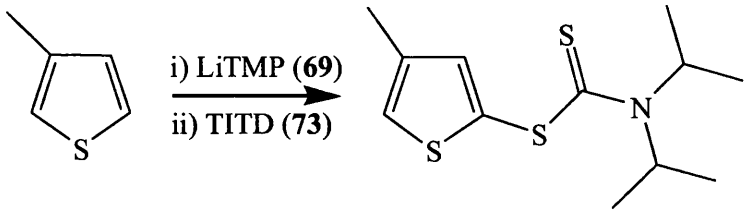


74 **75** **76**

Scheme 2.4: Bromine-lithium exchange of 74 and reaction with 73 (cf. Figure 2.11) *via* to give the dithiocarbamate 75, which was converted to the thiol 76 as reported by Jen *et al.* in 1982.[124]

It was thought that this would be an interesting electrophile to use, producing as it does a synthetically useful intermediate. The proposed reaction is shown in **Scheme 2.5.**

Compound **38** was lithiated with **69** as normal and stirred for 1 hour. A THF solution of **73** was added and the mixture was stirred overnight. Strongly acidic conditions were avoided during the workup in order to avoid destroying the dithiocarbamate product, using saturated aqueous ammonium chloride (NH_4Cl) to neutralise the mixture.



38 77

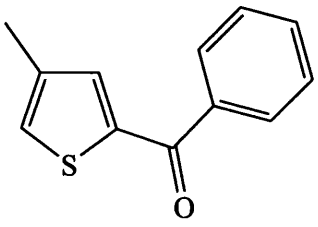
Scheme 2.5: Lithiation of 38 and reaction with 73 to di-*iso*-propyldithiocarbamic acid 4-methyl-2-thienyl ester (77).

After evaporation ^{1}H NMR analysis ($CDCl_3$, 25 °C) of the crude reaction mixture showed the two expected singlets in the aromatic region of the spectrum and there was no indication of the presence of the doublets that would indicate the presence of the unwanted isomer (cf. **Figure 2.5**). The CH protons of the two *iso*-propyl groups gave a very broad signal at δ = 4.7-5.2 ppm and the CH_3 protons of the two *iso*-propyl groups gave a broad signal at δ = 1.0-1.7 ppm. This was expected due to the restricted rotation of the two *iso*-propyl groups due to the proximity of the two sulfur atoms.[67f] Internal standard GC analysis showed that 94 % of **38** had been consumed. The mixture was purified by column chromatography with neutral alumina as the stationary phase (again to avoid acidic conditions) and the product **77** was isolated in 35 % yield. The reason for the low yield was not clear as the majority of the starting material had been consumed, but when the reaction was repeated similar yields were obtained. The product was not amenable to GC analysis, and therefore the yield of the reaction could not be calculated by GC.

The product **77**, which to the knowledge of the author had not previously been reported, was recrystallised from Et_2O/hexane. ^{1}H NMR analysis of the pure sample again showed a broad signal at δ = 1.0-1.7 ppm corresponding to the CH_3 groups of the *iso*-propyl groups and a very broad signal at δ = 4.7-5.2 ppm corresponding to the CHs of the *iso*-propyl groups. When the NMR was run at higher temperatures the signals of the *iso*-propyl hydrogens were much more well-defined due to the increase in available energy overcoming the restriction of rotation.[67f] ^{1}H and ^{13}C NMR spectra both correlated well with predicted signal values and there was no indication of the presence of the unwanted 2-substituted isomer. High resolution MS analysis (ES^+) showed a peak at *m/z* = 274.0751 which correlated well with the calculated mass of the protonated form of **77**, which was 274.0752, and microanalysis results correlated well with the calculated values. More detailed characterisation information can be found in the experimental section.

In conclusion, even though the isolated yield was low, the novel compound **77** was obtained in high purity by lithiation of **38** with **69** and reaction with **73** and there was no indication at any point of the presence of the unwanted isomer. As this reaction was not essential to the project the reaction was not optimised and the conversion of **76** to the corresponding thiol was not carried out.

2.6.3 Synthesis of (4-methyl-2-thienyl)phenylmethanone.

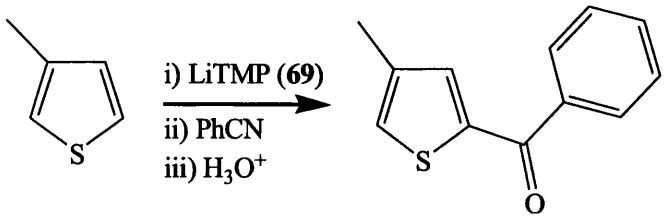


78

Figure 2.12: (4-methyl-2-thienyl)phenylmethanone (78).

(4-Methyl-2-thienyl)phenylmethanone (**78**, **Figure 2.12**) was reported by Spurlock in 1952[126] and Barrett in 2002.[73a] In both cases **78** was synthesised from **38** *via* Friedel-Crafts acylation and was obtained in good to moderate yields as a mixture with the 2,3-disubstituted isomer from which, Barrett states, **78** could not be separated.[73a]

It was thought that **78** could be synthesised selectively by lithiating **38** with **69** and subsequent reaction with benzonitrile which, according to literature examples,[127] would yield **78** (*via* an imine intermediate) upon aqueous workup. The reaction is shown in **Scheme 2.6**.



38 **78**

Scheme 2.6: Lithiation of 38 and reaction with benzonitrile (PhCN) followed by aqueous workup to form (4-methyl-2-thienyl)phenylmethanone (78).

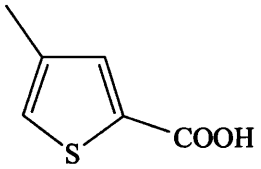
Compound **38** was lithiated with **69** in the usual way and PhCN (1 mol. eq.) was added. After aqueous workup and purification by column chromatography and recrystallisation **78** was isolated as white crystals in 91 % yield. The pure sample was

used to calculate the yield of the reaction *via* internal GC standard analysis and the yield was found to be 99 %, showing no evidence of the presence of the unwanted isomer.

^{1}H NMR analysis of the sample was consistent with predictions and showed no evidence of the presence of the unwanted isomer. ^{13}C NMR analysis showed the expected carbonyl carbon signal at δ = 188.7 ppm and no indication of the unwanted isomer. IR analysis showed a carbonyl peak. High resolution MS analysis (ES^{+}) showed a peak at *m/z* = 203.0523 which correlated well with the calculated mass of the protonated form of **78**, which was 203.0525. More detailed characterisation data are given in the experimental section.

In conclusion, it is possible to synthesise **78** with high selectivity and in high yield by the convenient one-pot lithiation of **38** with **69** and subsequent reaction with PhCN.

2.6.4 Synthesis of 4-methylthiophene-2-carboxylic acid

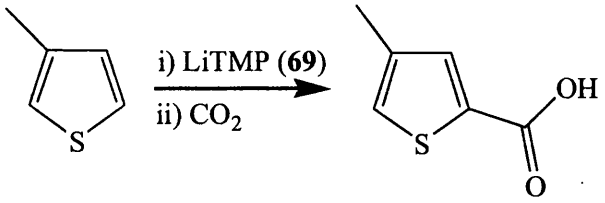


79

Figure 2.13: 4-methylthiophene-2-carboxylic acid (79)

The preparation of 4-methylthiophene-2-carboxylic acid (**79**, **Figure 21.3**) has been reported several times, both *via* the reaction of other 2-substituted-4-methylthiophenes[59,65,69,128] and *via* metalation of **38** with sodium in the presence of alkyl halides and reaction with CO_2.[129] The examples involving metalation of **38** are all over 50 years old and, although a high selectivity is reported, they are said to give very low yields. Aldrich have recently started offering **79** commercially in high purity but when contacted they informed the author that their synthetic method was confidential.

It was thought that **79** could be synthesised selectively by lithiating **38** with **69** and subsequent reaction with solid carbon dioxide which, according to literature examples,[129,130] would yield **79** upon aqueous workup. The reaction is shown in **Scheme 2.7**.



38 79

Scheme 2.7: Lithiation of 38 and reaction with CO_2 to form 4-methylthiophene-2-carboxylic acid (79).

Compound **38** was lithiated with **69** in the usual way and stirred for 1 hour. The THF solution of lithiated **38** was added to a slurry of excess solid CO_2 in THF and the mixture was stirred overnight. The mixture was quenched with saturated aqueous ammonium chloride solution. The aqueous phase, containing a carboxylate salt of **79**, was separated and acidified at which point the product **79** precipitated out as a white solid. Upon extraction with Et_2O and recrystallisation **79** was isolated as white crystals in 75 % yield. The ^1H NMR spectrum showed a very broad signal at δ = 8.3-10.5 ppm corresponding to the carboxylic acid proton and the rest of the spectrum correlated well with predictions. There was no indication that the unwanted 2-substituted isomer was present. ^{13}C NMR analysis showed the expected carboxylic acid carbon signal at δ = 168.3 ppm and correlated well with predictions. There was no indication that the unwanted 2-substituted isomer was present. IR analysis showed a very broad OH absorption and a carbonyl peak. High resolution MS analysis (ES^+) showed a peak at *m/z* = 160.0427 which correlated exactly with the calculated value for the $[M+NH_4]^+$ ion of **79**. More detailed characterisation data can be found in the experimental section.

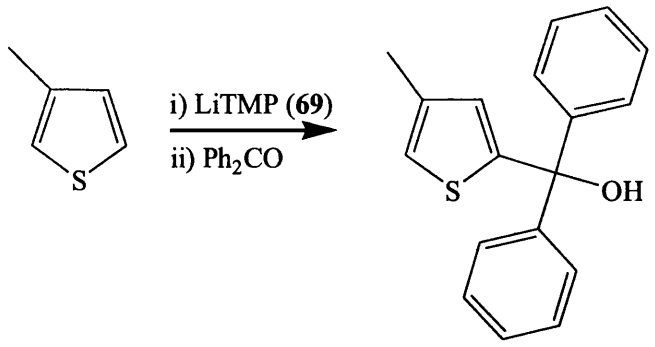
In conclusion, it is possible to synthesise **79** with high selectivity and in high yield by the convenient one-pot lithiation of **38** with **69** and subsequent reaction with CO_2.

2.6.5 Synthesis of (4-methyl-2-thienyl)diphenylmethanol.

Benzophenone (Ph_2CO) is a well-known electrophile in lithiation reactions of heterocycles.[131] It was thought this would be an interesting electrophile to try both for its proven utility in these reactions and because of its large size which, it was hoped, would further increase selectivity.

Compound **38** was lithiated with **69** in the usual way and stirred for 1 hour. Ph_2CO (1 mol. eq.) in solution in THF was added and the mixture was stirred overnight. Following acidic workup and purification by column chromatography

(4-methyl-2-thienyl)diphenylmethanol (**80**) was isolated as off-white crystals in 85 % yield and 97 % purity (GC). The reaction is shown in **Scheme 2.8**.



38 **80**

Scheme 2.8: Lithiation of 38 and reaction with Ph_2CO to form (4-methyl-2-thienyl)diphenylmethanol (80).

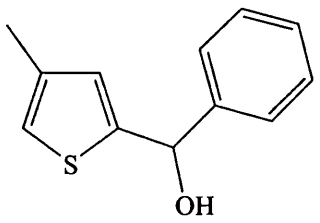
The sample was used to calculate the yield of the reaction by internal standard GC analysis. The yield was 98.4 %. There was no confirmed indication of the presence of the unwanted isomer in the GC trace, which is not surprising given the bulkiness of the electrophile, but there were several very small peaks in the GC trace that added up to the 3 % impurity. It is possible that one of these peaks was the unwanted isomer, but if so it was present in a negligible amount.

^1H NMR analysis showed the expected OH signal at $\delta = 2.83$ ppm which exchanged with D_2O, and the spectrum correlated well with predictions. There was no indication of the presence of the unwanted isomer. ^{13}C NMR analysis correlated well with predictions. IR analysis showed a broad OH absorption. High resolution MS analysis (EI^+) showed a molecular ion peak at $m/z = 280.0917$, which correlated well with the calculated molecular ion value of 280.0916. More detailed characterisation data are given in the experimental section.

The off-white crystals of **80** decomposed in air over time to form a purple solid. This was thought to be due to the stability of the triarylmethyl cation but was not investigated.

In conclusion, it is possible to synthesise the novel compound **80** with high selectivity and in high yield by the convenient one-pot lithiation of **38** with **69** and subsequent reaction with Ph_2CO.

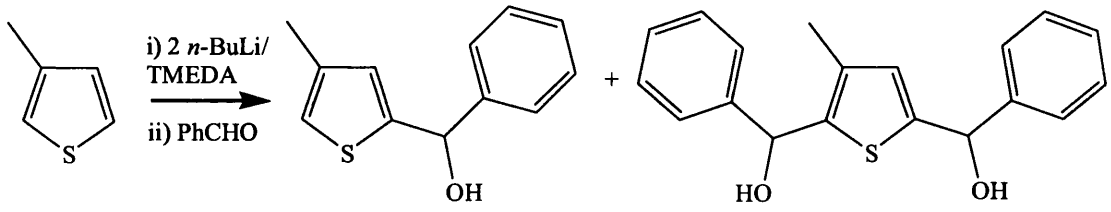
2.6.6 *Synthesis of (4-methyl-2-thienyl)phenylmethanol*



81

Figure 2.14: (4-Methyl-2-thienyl)phenylmethanol (81)

(4-Methyl-2-thienyl)phenylmethanol (**81**, **Figure 2.14**) was reported by Agarwal in 2004 as a by-product of the 2,5-dilithiation of **38** and subsequent reaction with benzaldehyde (PhCHO) to synthesise 2,5-*bis*-(hydroxymethylphenyl)-3-methylthiophene (**82**). The reaction as reported by Agarwal is shown in **Scheme 2.9**.[132]



38 **81** **82**

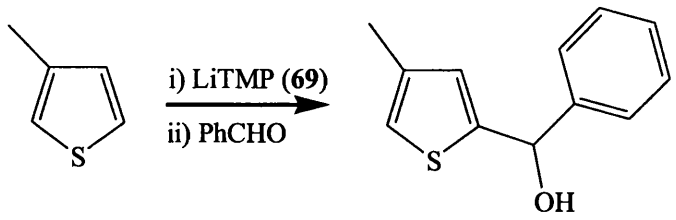
Scheme 2.9: Synthesis of 82 with 81 as a by-product as reported by Agarwal *et al.* in 2004.[132]

As **81** was not the desired product the characterisation data were not reported by Agarwal. This is, to the best of the author's knowledge, the only occurrence of **81** in the literature.

As PhCHO is a common electrophile in organolithium reactions,[130b,132,133] it was decided to attempt to synthesise **81** selectively and in high yield via lithiation of **38** with **69**.

Compound **38** was lithiated with **69** in the usual way and stirred for 1 hour. Benzaldehyde (1 mol. eq.) was added and the mixture was stirred overnight. Following acidic workup and purification by column chromatography

(4-methyl-2-thienyl)phenylmethanol (**81**) was isolated as light orange crystals in 79 % yield. The product was not amenable to analysis by GC. ^{1}H NMR analysis of the crude and purified samples showed no trace of the unwanted 2-substituted isomer. The reaction is shown in **Scheme 2.10**.



38 **81**

Scheme 2.10: Lithiation of 38 and reaction with PhCHO to form (4-methyl-2-thienyl)phenylmethanol (81).

^{1}H NMR analysis showed the expected OH signal at δ = 2.29 ppm which exchanged with D_2O, and the spectrum correlated well with predictions and with the spectrum of **79**, as would be expected. ^{13}C NMR analysis correlated well with predictions and with **79**. IR analysis showed a broad OH absorption. High resolution MS analysis (EI) showed a peak at *m/z* = 203.0521, which correlated well for the calculated mass of the $[M-H]^+$ ion of **81**, which was 203.0525. More detailed characterisation data can be found in the experimental section. Within a few days the sample had become a dark orange oil suggesting decomposition of some kind. The presence of an impurity would explain the orange colour of the freshly prepared sample. This was not investigated. If it was necessary to store this compound it could be stored as a protected derivative.

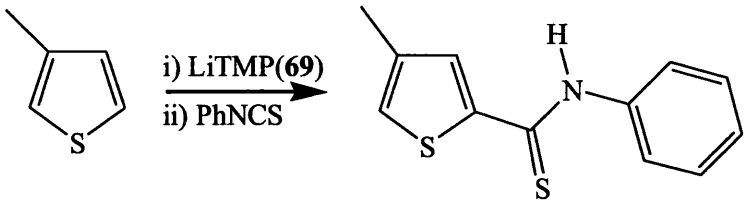
In conclusion, it is possible to synthesise **81** with high selectivity and in high yield by the convenient one-pot lithiation of **38** with **69** and subsequent reaction with PhCHO.

2.6.7 Synthesis of 4-methylthiophene-2-carbothioic acid phenylamide.

Phenyl isothiocyanate (PhN=C=S or PhNCS) has been used as an electrophile in lithiation reactions.[130b,134] Reactions of organolithium compounds with PhNCS yield carbothioic acid phenylamide derivatives.

Compound **38** was lithiated with **69** in the usual way and stirred for 1 hour. PhNCS (1 mol. eq.) was added and the mixture was stirred overnight. Following acidic workup

and purification by evaporation of the PhNCS and passing through a short silica plug 4-methylthiophene-2-carbothioic acid phenylamide (**83**) was isolated as bright yellow crystals in 76 % yield. The product was not amenable to analysis by GC. NMR analysis of both the crude and pure materials showed no trace of the unwanted 2-substituted isomer. The reaction is shown in **Scheme 2.11**.



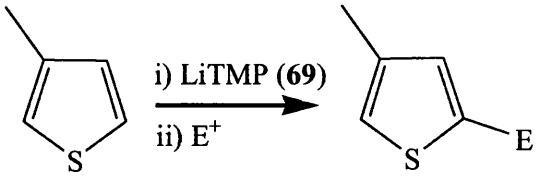
38 **83**

Scheme 2.11: Lithiation of 38 and reaction with PNCS to form 4-methyl-2-thienylcarbothioic acid phenylamide (83).

^{1}H NMR analysis showed the expected NH signal at $\delta = 8.84$ ppm which exchanged with D_2O, and the spectrum correlated well with predictions. ^{13}C NMR analysis correlated well with predictions. Microanalysis results correlated well with calculated values. High resolution MS analysis (ES^+) showed a peak at $m/z = 234.0406$, which correlated exactly with the calculated mass of the protonated form of **83**. More detailed characterisation data can be found in the experimental section.

In conclusion, it is possible to synthesise the novel compound **83** with high selectivity and in high yield by the convenient one-pot lithiation of **38** with **69** and subsequent reaction with PhNCS.

2.7 Summary of results.



38 **84**

Scheme 2.12: Lithiation of 38 with 69 and reaction with electrophiles to form a variety of selectively 2-substituted-4-methylthiophenes represented by the generic structure 84. E represents the group that is introduced at the 2-position using its electrophilic precursor E^+.

The work reported in this chapter is represented in **Scheme 2.12**. Compound **38** has been lithiated with **69** and subsequently reacted with a range of electrophiles to give a range of selectively 2-substituted-4-methylthiophenes (represented by the general structure **84,** where E is the group introduced into the 2-position *via* reaction with an electrophilic precursor E^+) in high yields. The results are shown in **Table 2.5.**

	Electrophile	E^+	Selectivity[a]	% Yield[b].	Product
1	MeI	Me	72:1	73 (98)	**23**
2	NBS	Br	12.6:1	46	**48**
3	DMF	CHO	35.5:1	89 (100)	**51**
4	TITD	$^iPr_2NCSS$	-	35	**77**
5	PhCN	PhCO	-	91 (99)	**78**
6	CO_2	COOH	-	75	**79**
7	Ph_2CO	Ph_2COH	-	85 (98)	**80**
8	PhCHO	PhCHOH	-	79	**81**
9	PhNCS	PhNCS	-	76	**83**

Table 2.5: Results of the lithiation of 38 with 69 and subsequent reactions with electrophiles to selectively introduce a group (E^+) at the 5-position of 38 to give a 2-substituted-4-methylthiophene product (cf. Scheme 2.12, see Sections 2.9.6 & 2.9.7 for experimental details).

a. **Selectivity is given as the ratio of the desired 2-substituted-4-methylthiophene to the unwanted 2-substituted-3-methylthiophene by-product calculated from the GC and NMR analyses. Where a number is not given there was no indication of the presence of the unwanted isomer.**
b. **Isolated yields of purified products. In such cases where the product was amenable to GC analysis the yield of the reaction was also calculated by internal standard GC analysis. The yield so calculated is shown in parentheses.**

2.8 Conclusion to Chapter 2.

The lack of selectivity in the lithiation of relatively unhindered 3-substituted thiophenes has been a long-standing problem in heterocyclic chemistry from the 1950s up until the present day.

Lithiation of unhindered 3-methylthiophene (**38**) with lithium 2,2,6,6-tetramethylpiperidide (LiTMP, **69**) takes place highly selectively at the 5-position due to the steric bulk of the lithiating reagent. Reaction with a variety of electrophiles has been shown to give the corresponding 2-substituted-4-methylthiophenes in high yield and high selectivity. This selectivity is very high even when relatively unhindered electrophiles such as iodomethane (MeI) and *N*,*N*-dimethylformamide (DMF) are used, and when bulkier electrophiles are used there is no indication at all of the presence of the unwanted by-product in the product mixture.

The one exception to this was the bromination reaction, which was not as selective, possibly due to the competing 2-selective electrophilic bromination reaction that **38** is known to undergo, and was low yielding. Experiments with different brominating reagents failed to improve this reaction.

The reaction with tetra-*iso*-propylthiuram disulfide (TITD, **73**) was apparently selective but was low-yielding.

A manuscript for publication of this work has been prepared.

2.9 Experimental.

2.9.1 General experimental.

Melting point (mp) and boiling point (bp) determinations were carried out under atmospheric pressure on a Gallenkamp melting point apparatus and are reported uncorrected.

IR Spectra were obtained using a Perkin Elmer Spectrum One FT-IR spectrometer.

UV Spectra were obtained using a Unicam UV 300 UV-Visible spectrometer.

^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz, CPD and DEPT) and ^{19}F NMR (376MHz) spectra were measured with a Bruker AC400 spectrometer with tetramethylsilane as reference. Peaks were assigned to the best of the author's ability with the aid of predictions from ChemDraw 7.0 but were not rigorously confirmed.

Fluorescence measurements were carried out using a Perkin Elmer LS 50B luminescence spectrometer.

Mass spectrometric analyses were carried out by the EPSRC National Mass Spectrometry Service Centre, Grove Building, University of Wales Swansea, Swansea, SA2 8PP. www.swan.ac.uk/nmssc/. Data for electrospray (ES) electron impact (EI) and chemical ionisation (CI) spectra are presented firstly with the high resolution analysis of the molecular or pseudo-molecular ion compared to the calculated value followed by the most abundant peaks in every measured spectrum with fragment assignments and relative intensities given in brackets. Fragments were assigned to the best of the author's ability but were not rigorously confirmed.

Microanalyses were carried out by Warwick Analytical Service, University of Warwick Science Park, Barclays Venture Centre, Sir William Lyons Rd., Coventry CV4 7EZ. www.warwickanalytical.co.uk. Data are given as the measured percentage values compared to the calculated values.

X-Ray crystallographic analyses were carried out by the EPSRC National Crystallography Service School of Chemistry, University of Southampton, Southampton, SO17 1BJ. http://www.ncs.chem.soton.ac.uk

Column chromatography was carried out with silica gel 60A (35-70μm particle size, obtained from Fischer chemicals) or activated neutral alumina (Brockmann I, Standard grade, approx. 150 mesh, 58 Å) as indicated in the individual procedures. TLC analyses were carried out on Whatman aluminium silica gel plates and visualised by ultraviolet light.

Chemicals were obtained from Aldrich, Fluka, Lancaster and Apollo chemicals, and were used as supplied unless GC analysis showed appreciable impurities.

Butyllithiums were estimated by the Gilman double titration method[101]

Tetrahydrofuran was dried by filtration through activated alumina, stirring overnight with calcium hydride and distillation from sodium benzophenone ketyl.

All other solvents were dried according to standard methods.[137]

Reduced pressure distillations were carried out using a water aspirator (15 mm Hg).

2.9.2 *GC conditions.*

Instrument	Hewlett Packard HP5890 Series II
	Gas Chromatograph with HP3396 Series II integrator.
Column	Zorbax ZB-5 5 % Phenyl 95 % Dimethylpolysiloxane
	30 m length 0.32 mm i.d.
Injection Mode	Splitless. Purge on at 0.7 min.
Injection Volume	0.5 µL
Injector Temperature	300 °C
Detector Temperature	300 °C
Temperature Programme	35 °C for 5 min
	Ramp A 3 °C/min to 75 °C. Hold for 5 min
	Ramp B 25 °C/min to 250 °C. Hold for 10 min.
Detector Attenuation	0
Detector Range	4
Integrator Attenuation	10
Integrator Chart Speed	0.2 cm/min
Integrator Area Rejection	50 1/8 µV-sec
Integrator Threshold	11
Integrator Peak Width	0.04 min

2.9.3 *GC Analyses: using the example of **23***.

2.9.3.1 Standard preparation.

2,4-Dimethylthiophene (**23**, 0.08 g) and tetradecane (0.05 g) were accurately weighed into a 10 mL volumetric flask. The solution was made up to 10 mL with diethyl ether. Standards were prepared in a similar way for all products.

2.9.3.2 Sample preparation.

The sample preparation procedure is given in the experimental procedures section.

2.9.3.3 Analysis of samples. [135]

Response factor calculations from the GC traces of the standard solutions were made according to **Equation 2.1**:

Rf = response factor, W_r = weight of **23**, W_{st} = weight of tetradecane, A_r = area of peak corresponding to **23**, A_{st} = area of tetradecane peak.

$$Rf = \frac{Wr \times Ast}{Wst \times Ar} \qquad \textbf{[Equation 2.1]}$$

The weight of **23** in the product sample was calculated using **Equation 2.2.**

$$Wr = \frac{Ar \times Wst}{Ast} \times Rf \qquad \textbf{[Equation 2.2]}$$

The yield of reaction was calculated by comparing the weight of product found in the sample to the weight of product that would be expected, calculated for 100 % yield relative to **38**.

2.9.4 *Lithiation of 3-methylthiophene with alkyllithiums and subsequent methylation.*

3-Methylthiophene (**38**, 0.294 g, 3.00 mmol) was dissolved in dry distilled THF (10 mL) in a septum-sealed 25 mL round bottom flask, which had previously been flushed with argon. The mixture was cooled in a dry ice and acetone bath for 30 min to ensure thorough cooling. The organolithium reagent solution (3.20 mmol) was added dropwise by syringe to the mixture, which was stirred for 1 h. Excess iodomethane (0.680 g, 4.79 mmol) was added dropwise by syringe and the mixture was stirred for 30 min, after which the cooling bath was removed and the mixture stirred for a further 90 min. An internal standard solution (5.00 mL of a 0.292 mol dm^{-3} solution of tetradecane in diethyl ether, 1.46 mmol) was added. Aqueous hydrochloric acid (2M, 20 mL) was added to quench the reaction. The mixture was swamped with diethyl ether (50 mL) and washed with saturated sodium hydrogen carbonate solution (20 mL) and saturated sodium chloride solution (20 mL). The organic phase was dried over anhydrous magnesium sulfate. An aliquot of the supernatant sample solution was analysed by GC to determine yield and the ratio of dimethylthiophenes. The results of these reactions are given in **Tables 2.1** and **2.2**.

2.9.5 *Lithiation of 3-methylthiophene with lithium amides and subsequent methylation.*

The appropriate dialkylamine (3.20 mmol) was dissolved in dry distilled THF (10 mL) in a septum-sealed 25 ml round bottom flask which had previously been flushed with argon. The mixture was cooled in a dry ice and acetone bath for 30 min to ensure thorough cooling. *tert*-Butyllithium (2 mL of a 1.7 mol dm^{-3} solution in pentane, 3.40 mmol) was added dropwise by syringe and the reaction mixture was stirred for 1 h. 3-Methylthiophene (**38**, 0.294 g, 3.00 mmol) was added by syringe, and the mixture was stirred for 1 h. Excess iodomethane (0.680 g, 4.79 mmol) was added dropwise by syringe and the mixture was stirred for 30 min, after which the cooling bath was removed and the mixture stirred for a further 90 min. An internal standard solution (5.00 mL of a 0.292 mol dm^{-3} solution of tetradecane in diethyl ether, 1.46 mmol) was added. Aqueous hydrochloric acid (2M, 20 mL) was added to quench the reaction. The mixture was

swamped with diethyl ether (50 mL) and washed with saturated sodium hydrogen carbonate solution (20 mL) and saturated sodium chloride solution (20 mL). The organic phase was dried over anhydrous magnesium sulfate. An aliquot of the supernatant sample solution was analysed by GC to determine yield and the ratio of dimethylthiophenes. The results of these reactions are given in **Table 2.2**.

2.9.6 Scaled-up synthesis and purification of 2,4-dimethylthiophene (23).

2,2,6,6-Tetramethylpiperidine (8.20 g, 58.0 mmol) was dissolved in dry distilled THF (100 mL) in a septum-sealed 250 ml round bottom flask which had previously been flushed with argon. The mixture was cooled in a dry ice and acetone bath for 30 min to ensure thorough cooling. *tert*-Butyllithium (35 mL of a 1.7 mol dm^{-3} solution in pentane, 59.5 mmol) was added dropwise by syringe and the reaction mixture was stirred for 1 h. 3-Methylthiophene (**38**, 5.40 g, 55.0 mmol) was added by syringe, and the mixture was stirred for 1 h. Excess iodomethane (12.5 g, 88.0 mmol)was added dropwise by syringe and the mixture was stirred for 30 min, after which the cooling bath was removed and the mixture stirred for a further 90 min. Aqueous hydrochloric acid (2M, 80 mL) was added to quench the reaction. The mixture was swamped with diethyl ether (120 mL) and washed with saturated sodium hydrogen carbonate solution (80 mL) and saturated sodium chloride solution (80 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, evaporated and made up to 200 ml in a volumetric flask. A 1 mL aliquot was taken, internal standard solution (1 mL of a 0.3 mol dm^{-3} solution of tetradecane in diethyl ether, 0.3 mmol) was added to the aliquot and the yield was determined by GC with reference to a standard solution made up with purified **23** and tetradecane). The remaining dark brown solution was treated three times with decolourising charcoal (approx. 2 g, stirred at room temp. for 20 min.) and evaporated to give a light green oil in 99 % yield (6.15 g, 54.9 mmol). The oil was distilled under atmospheric pressure to give **23** as a colourless liquid (97 % pure, bp 139 °C, 4.50 g, 73 %). Further characterisation details are given in Section 2.9.8.

Immediately upon removal from the organic phase, the HCl phase (pH = 1) was treated with 2M aqueous sodium hydroxide until the pH reached 14, at which point HTMP separated out as an oil. After being allowed to cool to room temperature the

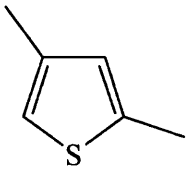
mixture was extracted with diethyl ether (4 x 50 mL). The ether phase was washed with saturated aqueous sodium chloride solution and dried with magnesium sulfate. Upon evaporation and distillation under reduced pressure HTMP was recovered as a colourless oil in 87 % yield (7.13 g, 50.5 mmol).

2.9.7 Reactions with different electrophiles.

2,2,6,6-Tetramethylpiperidine (0.452 g, 3.20 mmol) was dissolved in dry distilled THF (15 mL) in a sealed 50 mL round bottom flask which had previously been flushed with argon. The mixture was cooled in a dry ice and acetone bath for 30 min to ensure thorough cooling. *tert*-Butyllithium (2 mL of a 1.7 mol dm^{-3} solution in pentane, 3.40 mmol) was added dropwise by syringe and the reaction mixture was stirred for 1 h. 3-Methylthiophene (**38**, 0.294 g, 3.00 mmol) was added by syringe, and the mixture was stirred for 1 h. Electrophile (3.70 mmol, 7.40 mmol in the case of DMF- for further details see individual examples) was added dropwise by syringe or, if solid, dissolved in dry-distilled THF (10 mL) and added dropwise by syringe. The mixture was stirred overnight, warming to room temperature in the process. Aqueous hydrochloric acid (2M, 20 mL) was added to quench the reaction (for exceptions to this, see individual examples). The mixture was swamped with diethyl ether (50 mL) and washed with saturated sodium hydrogen carbonate solution (20 mL) and saturated sodium chloride solution (20 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and made up to 100 ml in a volumetric flask. If the product was amenable to analysis by GC, a 1 mL aliquot was taken, internal standard solution (0.50 mL of a 0.30 mol dm^{-3} solution of tetradecane in diethyl ether, 0.15 mmol) was added to the aliquot and the yield was determined by GC (with reference to a standard solution of the purified product and tetradecane). The remaining product solution was evaporated and the mixture was separated by column chromatography where necessary (see individual examples for details). The purified product was characterised as reported.

The results are given in **Table 2.5** and Sections 2.9.9-2.9.16.

2.9.8 *2,4-Dimethylthiophene (23).*

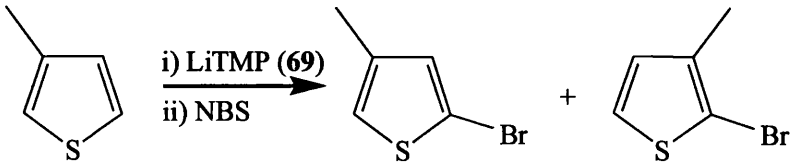


23

Figure 2.15: 2,4-dimethylthiophene (23)

The synthesis was carried out according to the procedure given in Section 2.9.6. Purified by distillation. Colourless liquid. bp 139 °C (lit.[65] 139 °C), 97.2 % pure by GC. GC yield = 98% (6.05 g, 53.9 mmol, cf. Section 2.9.6). Isolated yield = 73% (4.50 g, 40.2 mmol). Selectivity: 79:1 (**23**:**44**, GC, NMR). υ_{max} (film) /cm^{-1} 2919, 1440. δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.04 (3H, s, 2-C*H*$_3$), 2.32 (3H, s, 4-C*H*$_3$), 6.40 (1H, s, 3-*H*), 6.49 (1H, s, 5-*H*). δ_C (100 MHz; $CDCl_3$; Me_4Si) 15.7 (2-*C*H$_3$), 16.2 (4-*C*H$_3$), 118.6 (5-*C*H), 128.1 (3-*C*H), 138.0 (4-*C*), 140.0 (2-*C*). *m/z* (EI$^+$) = 111.0262 ([M-H]$^+$ C_6H_7S requires 111.0263). *m/z* (EI$^+$) = 112 ([M]$^+$ 72 %), 111 ([M-H]$^+$ 100 %), 97 ([M-CH_3]$^+$ 84 %), 77 (50 %), 45 (60%), 39 (45 %).

2.9.9 *2-Bromo-4-methylthiophene (48).*



38 **48** **70**

Scheme 2.13: Lithiation of 38 and reaction with NBS to give a 12.6:1 mixture of 48 and 70.

The synthesis was carried out according to the procedure given in Section 2.9.7. Reagent: NBS (0.658 g, 3.70 mmol). GC yield = 46.1% (0.244 g, 1.38 mmol) based on starting material consumed. This is the sum of both isomers. Selectivity; 12.6:1 (**48**:**70**, GC & NMR). Purified by removal of the unconsumed **38** by distillation under atmospheric pressure. Isolated as a brown oil. ν_{max} (film) /cm^{-1} 2922, 1408. *m/z* (EI$^+$) =

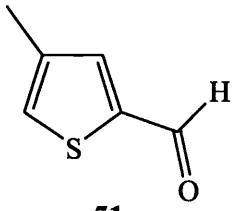
176.0, 178.0 in a ratio of 1:1 approx. (isotope peaks of $[M]^+$ 23 %, 25 %), 97 ($[M-Br]^+$ 66 %), 81 (28 %), 69 (45 %), 58 (54 %), 45 (100 %).

The NMR spectrum showed a mixture of **48** and **70** in a product ratio of 12.7:1 respectively. The NMR assignments are given separately.

48[79]: δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.03 (3H, s, C*H*$_3$), 6.56 (1H, s, 5-*H*), 6.68 (1H, s, 3-*H*). δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.05 (*C*H$_3$), 112.1 (2-*C*Br), 122.8 (5-*C*H), 133.7 (3-*C*H), 138.8 (4-*C*).

70[80c]: δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.01 (3H, s, C*H*$_3$), 6.60 (1H, d, J = 5.5 Hz 4-*H*), 6.96 (1H, d, J = 5.5 Hz, 5-*H*). δ_C (100 MHz; $CDCl_3$; Me_4Si) 15.51 (*C*H$_3$), 109.7 (2-*C*Br), 126.0 (5-*C*H), 129.7 (4-*C*H), 137.6 (3-*C*).

2.9.10 4-Methyl-2-thiophenecarboxaldehyde (51)

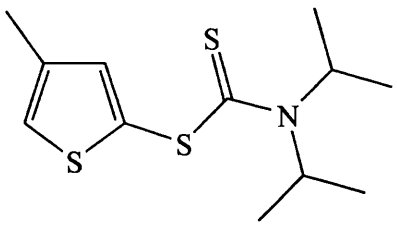


51

Figure 2.16: 4-Methyl-2-thiophenecarboxaldehyde (51).

The synthesis was carried out according to the procedure given in Section 2.9.7. Reagent: 2.2 eq. DMF (0.546 g, 7.48 mmol). Purified by passing through a short alumina plug with 50% Et_2O/hexane and subsequent reduced-pressure distillation. Clear colourless liquid. bp 224 °C, purity 97.3 % (GC). Selectivity; 35.5:1 (**51**:**72**, cf. **Scheme 2.3**, GC). GC yield = 100% (0.377 g, 3.00 mmol). Isolated yield = 89 % (0.335 g. 2.666 mmol). ν_{max} (film) /cm^{-1} 1661 (C=O). δ_H (400 MHz; $CDCl_3$; Me_4Si)[70] 2.24 (3H, s, C*H*$_3$), 7.30 (1H, s, 5-*H*), 7.50 (1H, s , 3-*H*), 9.78 (1H, s, C*H*O). δ_C (100 MHz; $CDCl_3$; Me_4Si)[123] 15.8 (*C*H$_3$), 131.5 (5-*C*H), 139.4 (3-*C*H), 139.6 (4-*C*), 144.0 (2-*C*), 183.0 (*C*HO). *m/z* (EI^+) = 125.0056 ($[M-H]^+$ C_6H_5OS requires 125.0056). *m/z* (EI^+) = 126 ($[M]^+$ 78 %), 125 ($[M-H]^+$ 100 %), 97 ($[M-CHO]^+$ 90 %), 69 (50 %), 53 (72 %), 45 (78 %), 39 (51 %)

2.9.11 *Di*-iso-*propyldithiocarbamic acid 4-methyl-2-thienyl ester (77).*

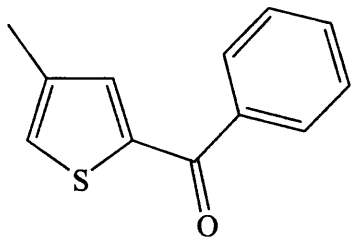


77

Figure 2.17: Di-*iso*-propyldithiocarbamic acid 4-methyl-2-thienyl ester (77).

The synthesis was carried out according to the procedure given in Section 2.9.7. Reagent: TITD (**73**, 1.30 g, 3.70 mmol). Workup was carried out with saturated ammonium chloride solution instead of HCl to avoid cleaving the dithiocarbamate ester group. Purified by column chromatography: alumina column, gradient elution (hexane up to 25 % Et_2O/hexane) and recrystallisation (Et_2O/hexane). Isolated yield = 35 % (0.286 g, 1.05 mmol). White solid (mp 112.0-112.8 °C). Anal. Found: C 52.6, H 6.92, N 5.01 %. Calc for $C_{12}H_{19}NS_3$: C 52.7, H 7.00, N 5.12 %. ν_{max} (film) /cm^{-1} 1319 (C=S). δ_H (400 MHz; $CDCl_3$;): 1.0-1.7 (12H, broad, gained definition at higher temperature, di-*iso*-propylamino C*H*$_3$),[67f] 2.22 (3H, s, thienyl C*H*$_3$), 4.7-5.2 (2H, very broad, gained definition at higher temperature, di-*iso*-propylamino C*H*),[67f] 6.96 (1H, s, thienyl 3-C*H*), 7.17 (1H, s, thienyl 5-C*H*). δ_C (100 MHz; $CDCl_3$; Me_4Si.) 16.3 (thienyl *C*H$_3$), 20.3 (gained definition at higher temperature, di-*iso*-propylamino *C*H$_3$),[67f] 56.4 (gained definition at higher temperature, di-*iso*-propylamino *C*H),[67f] 131.3 (thienyl 2-*C*), 131.6 (thienyl 5-*C*H), 140.3 (thienyl 4-*C*), 142.9 (thienyl 3-*C*H), 196.3 (C=S). *m/z* (ES^+) = 274.0751 ($[M+H]^+$ $C_{12}H_{20}NS_3$ requires 274.0751). *m/z* (EI^+) = 273 ($[M]^+$ 2%), 241 (10 %), 198 (16 %), 141 (90 %), 102 (93 %), 60 (66 %), 43 (100 %). *m/z* ($CI^+(NH_3)$) = 274 ($[M+H]^+$ 78 %), 242 (13 %), 212 (10 %), 146 (100 %).

2.9.12 (4-Methyl-2-thienyl)phenylmethanone (78).

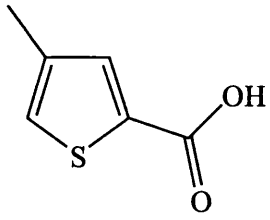


78

Figure 2.18: (4-Methyl-2-thienyl)phenylmethanone (78).

The synthesis was carried out according to the procedure given in Section 2.9.7. Reagent: benzonitrile (0.382 g, 3.70 mmol). GC yield = 99% (0.598 g, 2.97 mmol). Isolated yield = 91% (0.545 g, 2.70 mmol). Purified by column chromatography (alumina column, 10% Et_2O/hexane) and recrystallisation (Et_2O/hexane). White solid. mp 90.0-91.4 °C (lit.[126] 91-92 °C.). Purity 96 % (GC). ν_{max} (film) /cm^{-1} 1627 (C=O). δ_H (400 MHz; $CDCl_3$; Me_4Si) δ = 2.32 (3H, s, CH_3), 7.34 (1H, s, thienyl 5-C*H*), 7.47 (1H, s, thienyl 3-C*H*), 7.52 (2H, triplet, J = 8 Hz, phenyl *meta*-C*H*), 7.61(1H, t, J = 8 Hz, phenyl *para*-C*H*), 7.70 (2H, d, J= 8, phenyl *ortho*-C*H*). δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.0 (CH_3), 128.8 (phenyl *meta*-C*H*), 129.5 (phenyl *ortho*-C*H*), 130.6 (phenyl *para*-C*H*), 132.5 (thienyl 5-C*H*), 137.3 (thienyl 3-C*H*), 138.7 (phenyl 1-*C*), 139.2 (thienyl 4-*C*), 143.6 (thienyl 2-*C*), 188.7 (*C*O). *m/z* (ES^+) = 203.0523 ($[M+H]^+$ $C_{12}H_{11}S$ requires 203.0525). *m/z* (EI^+) = 202 ($[M]^+$ 19 %), 125 ($[M-Ph]^+$ 57 %), 105 ($[PhCO]^+$ 27 %), 77 ($[Ph]^+$ 100 %), 51 (76 %). *m/z* ($CI^+(NH_3)$) = 220 ($[M+NH_4]^+$ 25 %), 203 ($[M+H]^+$ 100 %).

2.9.13 4-Methylthiophene-2-carboxylic acid (79).

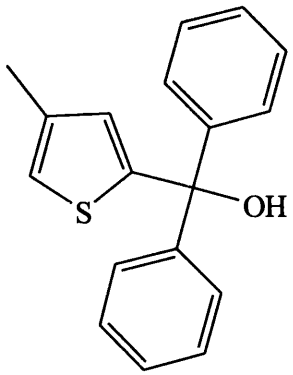


79

Figure 2.19: 4-methylthiophene-2-carboxylic acid (79).

The synthesis was carried out according to the procedure given in Section 2.9.7. Reagent: Excess solid CO_2 (approx. 2.5 g, slurried in THF (15 mL) to which the THF solution of lithiated **38** was added). Formed as the carboxylate salt. Isolated by treating the NH_4Cl phase with 2M HCl until pH = 1, when the product precipitated out as a white solid. Et_2O (3 x 100 mL) was added in which the white solid dissolved. Evaporation and recrystallisation (Et_2O/hexane) gave the product. Isolated yield = 75% (0.319 g, 2.25 mmol). White solid mp 119.7-121.5 °C. Purity = 95 % (GC). ν_{max} (film) /cm^{-1} 1660 (C=O), 2853 (broad OH). δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.24 (3H, s, C*H*$_3$), 7.14 (1H, s, 5-*H*), 7.65 (1H, s , 3-*H*), 8.3-10.5 (1H, s, very broad, COO*H*).). δ_C (100 MHz; $CDCl_3$; Me_4Si) 15.9 (*C*H$_3$), 130.31 (5-*C*H), 132.8 (2-*C*), 137.2 (3-*C*H), 139.3 (4-*C*), 168.3 (*C*OOH). *m/z* (ES^+) = 160.0427 ($[M+NH_4]^+$ $C_6H_{10}O_2NS$ requires 160.0427). *m/z* (EI^+) = 142 ($[M]^+$ 24 %), 125 ($[M-OH]^+$ 21 %), 97 (31 %), 45 (100 %). *m/z* (CI^+) 160 ($[M+NH_4]^+$, 100%), 142 ($[M]^+$ 80 %), 125 ($[M-OH]^+$ 22 %), 108 (23 %), 97 (20 %), 82 (24 %).

2.9.14 *(4-Methyl-2-thienyl)diphenylmethanol (80).*



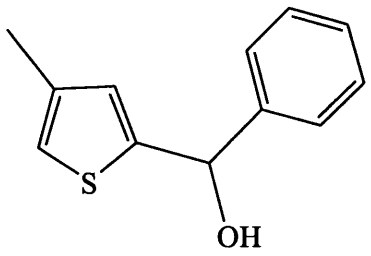
80

Figure 2.20: (4-Methyl-2-thienyl)diphenylmethanol (80).

The synthesis was carried out according to the procedure given in Section 2.9.7. Reagent: benzophenone (0.674 g, 3.70 mmol). Purified by column chromatography: silica column, gradient elution (hexane up to10% Et_2O/hexane) and recrystallisation (Et_2O/hexane). GC yield = 98% (0.825 g, 2.95 mmol). Isolated yield = 85% (0.701 g, 2.51 mmol). Off-white solid (mp 81.7- 83.2 °C). Purity = 97% (GC). Crystals turn purple over time. ν_{max} (film) /cm^{-1} 3419 (OH). δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.09 (3H, s, C*H*$_3$) 2.83 (1H, s, D_2O exch., O*H*), 6.44 (1H, s, thienyl 3-*H*), 6.74 (1H, s thienyl 2-*H*),

7.15-7.30 (10H, m, phenyl *H*). δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.3 (*C*H_3), 80.4 (*C*OH), 121.4 (thienyl 5-*C*H), 127.7, 128.0, 128.4 (phenyl *ortho*-*C*H, phenyl *para*-*C*H, phenyl *meta*-*C*H), 129.7 (thienyl 3-*C*H), 137.5 (thienyl 4-*C*), 147.0 (phenyl 1-*C*), 152.3 (thienyl 5-*C*). *m/z* (EI^+) = 280.0917 ($[M]^+$ $C_{18}H_{16}OS$ requires 280.0916). *m/z* (EI^+) = 280.1 ($[M]^+$ 23 %), 263 ($[M\text{-}OH]^+$ 24 %), 247 (23 %), 203 ($[M\text{-}Ph]^+$ 73 %), 175 (72 %), 125 (69 %), 105 (87 %), 96.9 (27 %), 77 ($[Ph]^+$ 100 %). *m/z* ($CI^+(NH_3)$) 280 ($[M]^+$ 10 %), 263 ($[M\text{-}OH]^+$ 100 %).

2.9.15 4-(Methyl-2-thienyl)phenylmethanol (81)

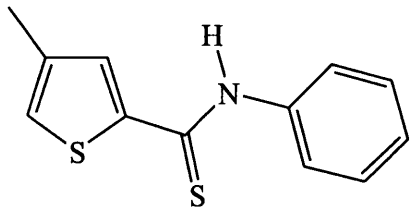


81

Figure 2.21: (4-Methyl-2-thienyl)phenylmethanol (81).

The synthesis was carried out according to the procedure given in Section 2.9.7. Reagent: Benzaldehyde (0.393 g, 3.70 mmol). Purified by column chromatography: silica column, eluted with 10% Et_2O/hexane. Isolated yield = 79% (0.483 g, 2.37 mmol). Light orange solid (mp 46.7-48.0 °C). Turns orange and loses solidity over the course of a few days. ν_{max} (film) /cm^{-1} 3310 (OH). δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.10 (3H, s, C*H*$_3$), 2.29 (1H, s, D_2O exch., O*H*), 5.94 (1H, s, C*H*OH), 6.15 (1H, s, thienyl 3-*H*), 6.77 (1H, s, thienyl 5-*H*), 7.20-7.45 (5H, m, Ph*H*). δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.2 (*C*H_3), 76.9 (*C*HOH), 121.0 (thienyl 5-*C*H), 127.3, 127.8, 128.3, 129.6 (thienyl 3-*C*H, phenyl *ortho*-*C*H, phenyl *para*-*C*H, phenyl *meta*-*C*H), 137.4 (thienyl 4-*C*), 141.6 (phenyl 1-*C*), 146.3 (thienyl 2-*C*). *m/z* (EI^+) = 203.0521 ($[M\text{-}H]^+$ $C_{12}H_{11}OS$ requires 203.0525). *m/z* (EI^+) = 204 ($[M]^+$ 26 %), 203 ($[M\text{-}H]^+$ 62 %), 187 ($[M\text{-}OH]^+$ 65 %), 171 (51 %), 127 ($[M\text{-}Ph]^+$ 105 (80 %), 99 (100 %), 77 ($[Ph]^+$ 91 %). *m/z* ($CI^+(NH_3)$) 203 ($[M\text{-}H]^+$ 10 %), 189 ($[M\text{-}CH_3]^+$ 77 %), 87 ($[M\text{-}OH]^+$ 100 %).

2.9.16 4-Methyl-2-thiophenecarbothioic acid phenylamide (83).



83

Figure 2.22: 4-Methyl-2-thiophenecarbothioic acid phenylamide (83).

The synthesis was carried out according to the procedure given in Section 2.9.7. Reagent: PhNCS (0.500 g, 3.70 mmol). Purified by evaporation of liquids, passing through a short silica column eluted with 20% Et_2O/hexane to remove coloured impurities and subsequent recrystallisation (Et_2O/hexane). Isolated yield = 76% (0.531 g, 2.28 mmol). Bright yellow solid (mp 104.2-105.0 °C). Anal. Found: C 61.60, H 4.69, N 5.88 %. Calc. for $C_{12}H_{11}NS_2$: C 61.81, H 4.75, N 6.00 %. ν_{max} (film) /cm^{-1} 3231 (C=S). δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.18 (CH_3), 7.06 (1H, s, thienyl 3-*H*), 7.18 (1H, t, *J* = 8 Hz, phenyl *para-H*), 7.29 (3H, m, phenyl *ortho-H* + thienyl 5-*H*), 7.55 (2H, triplet, *J* = 8 Hz, phenyl *meta-H*), 8.84 (1H, s, D_2O exch., N*H*). δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.2 (CH_3), 124.6 (phenyl *ortho-C*H + thienyl 2-*C*), 127.4 (thienyl 5-*C*H), 129.0 (phenyl *para-C*H), 129.4 (phenyl *meta-C*H + thienyl 3-*C*H), 139.0, 139.2 (thienyl 4-*C*, phenyl 1-*C*), 188.3 (*C*=S). *m/z* (ES^+) = 234.0406 ($[M+H]^+$ $C_{12}H_{12}NS_2$ requires 234.0406). *m/z* (EI^+) = 233 ($[M]^+$ 62 %), 200 (41 %), 141 (100%), 110 (28 %), 97 (40 %), 77 ($[Ph]^+$ 52 %). *m/z* (CI^+) 234 ($[M+H]^+$ 100 %), 202 (22 %).

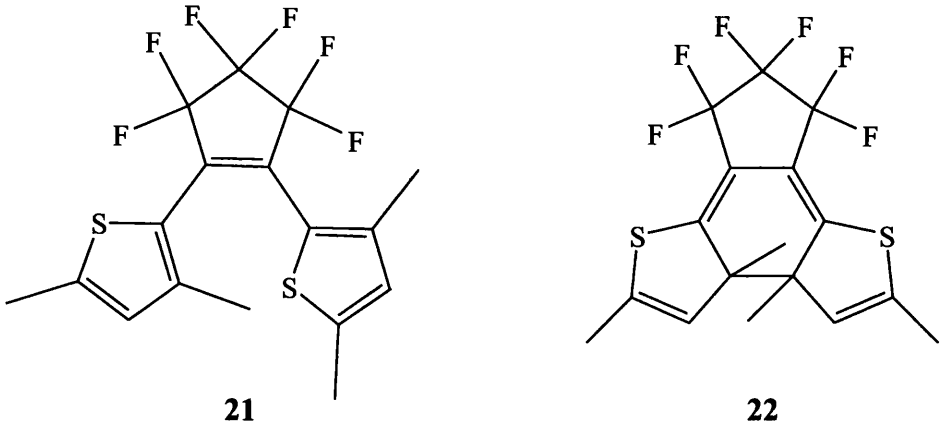
Chapter Three:

Synthesis and evaluation of 21.

Synthesis and reaction of protected amines.

3.1. Introduction.

The need for a linkable photochromic acceptor molecule that would undergo switchable RET with *N*-methylacridone (**1**) has been discussed in the previous chapters. The photochromic molecule that was selected as a starting point, **21**, is shown in **Figure 3.1** (cf. Section 1.6.1).



21 **22**

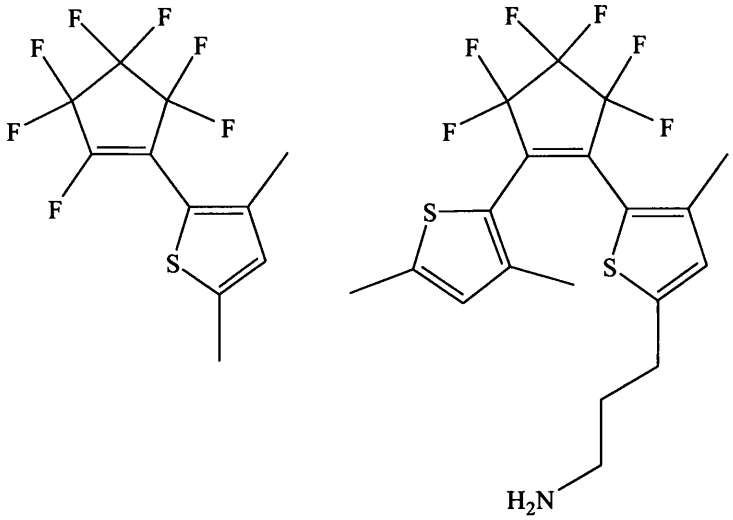
Figure 3.1: The open (21) and closed (22) forms of the photochromic molecule that was selected from the literature as a viable switchable RET acceptor for 1 as reported by Uchida & Irie in 1995. [50]

As discussed in Section 1.6.2, the reported synthesis of **21** (**Scheme 1.11**) involved a disubstitution of octafluorocyclopentene (**13**) with lithiated 2,4-dimethylthiophene (**23**). This was complicated by the unavailability of **23** and the difficulty involved in synthesising it. In order to overcome this problem a regioselective and high-yielding method for the synthesis of **23** *via* lithiation of 3-methylthiophene (**38**) with lithium 2,2,6,6-tetramethylpiperidide (**69**) was developed.

As it was now possible to synthesise **23** in high purity and high yield the next stage of this project, the synthesis of **21**, could be attempted. Once **21** had been synthesised it was necessary to measure its photochromic characteristics and evaluate the viability of the closed form **22** (**Figure 3.1**) as a RET acceptor for the fluorophore *N*-methylacridone (**1**). This would be done by calculating the Förster distance (R_0) as explained in sections 1.3.2 and 1.3.3.

It was also necessary to synthesise **46** (**Figure 3.2**) and confirm its effectiveness as an electrophile in lithiation reactions. This work is reported in the first part of this chapter.

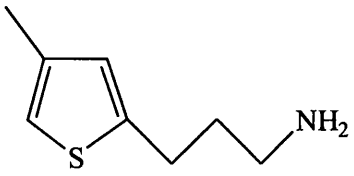
After this evaluation, the subsequent stage of this work involved attempting to synthesise the linkable target molecule **45** (**Figure 3.2**).



46 45

Figure 3.2: The monosubstituted perfluorocyclopentene 46 and the proposed linkable photochromic acceptor molecule 45.

The initial proposed syntheses of **45**, given in section 1.11, involved the synthesis of the starting material 3-(4-methyl-2-thienyl)-1-propylamine (**47, figure 3.3**), the protection of the amine functionality, reaction with the monothienyl perfluorocyclopentene **46** and subsequent deprotection to yield **45**.



47

Figure 3.3: The required starting material 3-(4-methyl-2-thienyl)-1-propylamine (47).

Two methods for the synthesis of **47** had been devised. The first planned synthesis of **47** (Section 1.11.1, **Scheme 1.24**) involved the synthesis of 2-bromo-4-methylthiophene (**48**) and subsequent Heck coupling of **48** with acrylonitrile (**49**). As has been reported in Chapter 2 (section 2.5.2), the synthesis of **48** from **38** was low yielding and suffered from low selectivity, possibly due to the occurrence of a competing side-reaction. Consequently, this synthetic route to **47** was not pursued.

The second planned synthesis of **47** (Section 1.11.2, **Scheme 1.25**) involved the synthesis of 4-methyl-2-thiophenecarboxaldehyde (**51**) which could be functionalised to form **47**. As has been reported in Chapter 2 (Section 2.5.3), the highly selective and high-yielding synthesis of **51** was achieved *via* the lithiation of **38** with **69** and

subsequent reaction with DMF. The subsequent synthesis of **47** from **51** is reported in this chapter, as are the syntheses of several protected derivatives of **47**.

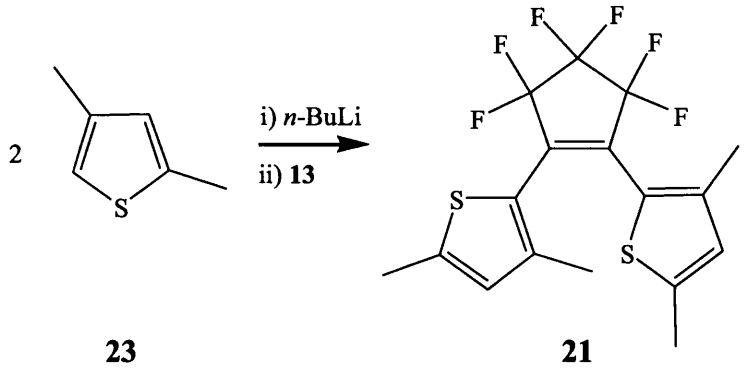
The final stage of the synthesis of **45** involved the reaction of **46** with the protected derivatives of **47**, which is also reported in this chapter.

3.2. Synthesis and evaluation of 21.

3.2.1. Synthesis of 21.

The synthesis of **21**, reported by Uchida and Irie,[50] was carried out. As octafluorocyclopentene (**13**) is volatile and was obtained in a pressurised canister, it was collected in a cooled trap and then dissolved in a known volume of THF before addition to the reaction mixture.

Compound **23** was lithiated with *n*-BuLi, and **13** was added. The reaction was quenched with HCl and worked up in the usual manner. GC analysis of the product solution showed a clean reaction mixture with one product peak. After purification with column chromatography and recrystallisation **21** was obtained in 78 % yield as bright yellow crystals. The reaction is shown in **Scheme 3.1.**



23 **21**

Scheme 3.1: The reaction of 13 with 2 mole equivalents of lithiated 23 to yield the photochromic molecule 21 as reported by Uchida and Irie in 1995.[50]

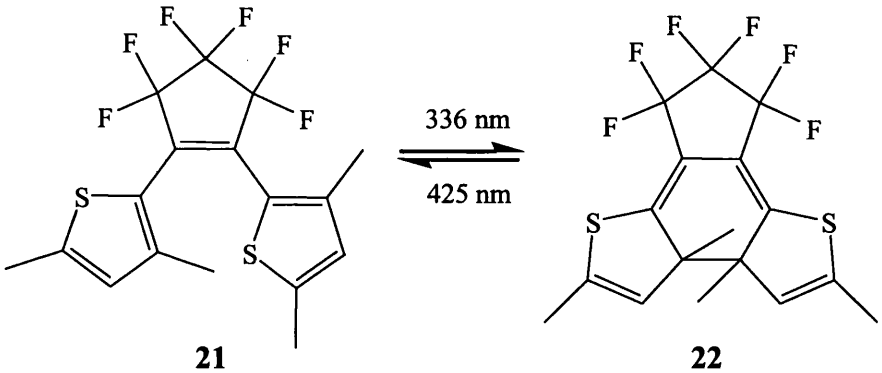
The ^{1}H NMR analysis correlated well with published data.[50] ^{13}C NMR analysis correlated well with predictions. The carbons of the perfluorocyclopentene moiety showed the expected splitting patterns and correlated well with published ^{13}C NMR data for the starting material **13**.[136] ^{19}F NMR analysis correlated well with the published ^{19}F NMR data for **13**.[136] High-resolution mass spectroscopic analysis (EI^{+}) showed a peak at

m/z = 396.0436 which correlated exactly with the calculated value of the mass of the molecular ion. More detailed characterisation data can be found in the experimental section.

In conclusion, the literature report that **21** can be synthesised conveniently and in high yield by the reaction of two mole equivalents of **23** with **13** *via* lithiation has been confirmed.

3.2.2. *Photochromism of 21.*

The reported photochromic conversion of **21** to the closed form **22** upon irradiation (**Scheme 3.2**) was investigated.



21 **22**

Scheme 3.2: The thermally irreversible photochromic conversion of 21 to 22.[50]

UV-Vis Spectroscopic analysis of a colourless methanol (this was necessary due to the reported quantum yield value of *N*-methylacridone being for a methanol solution) solution of **21** (7.32×10^{-5} mol dm^{-3}) showed an absorption at $\lambda = 345$ nm, which correlated well with the published value for **21** of $\lambda = 336$ nm in hexane. The solution was irradiated with UV light ($\lambda = 366$ nm) for 15 minutes, after which time it had developed a yellow colour. UV-Vis Spectroscopic analysis showed a pronounced decrease in the absorption at $\lambda = 345$ nm and the appearance of a new peak at $\lambda = 437$ nm, correlating well with the published value for **22** of $\lambda = 425$ nm in hexane. The colourless solution of **21** is shown in **Figure 3.4a** and the yellow solution of the photoconverted form **22** is shown in **Figure 3.4b**. The UV spectral change is shown in **Figure 3.5**.

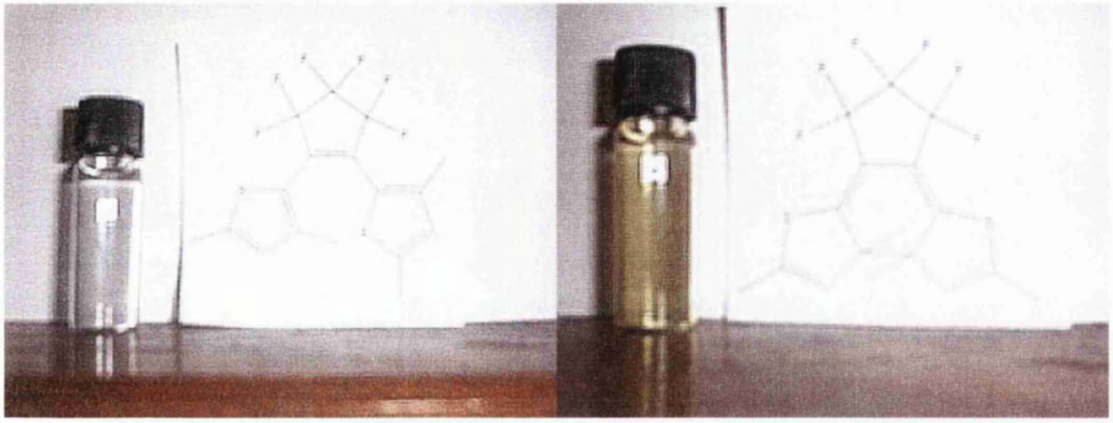


Figure 3.4a: The colourless solution of the A-form of the photochromic molecule (21)

Figure 3.4b: The yellow solution of the B-form of the photochromic molecule (22)

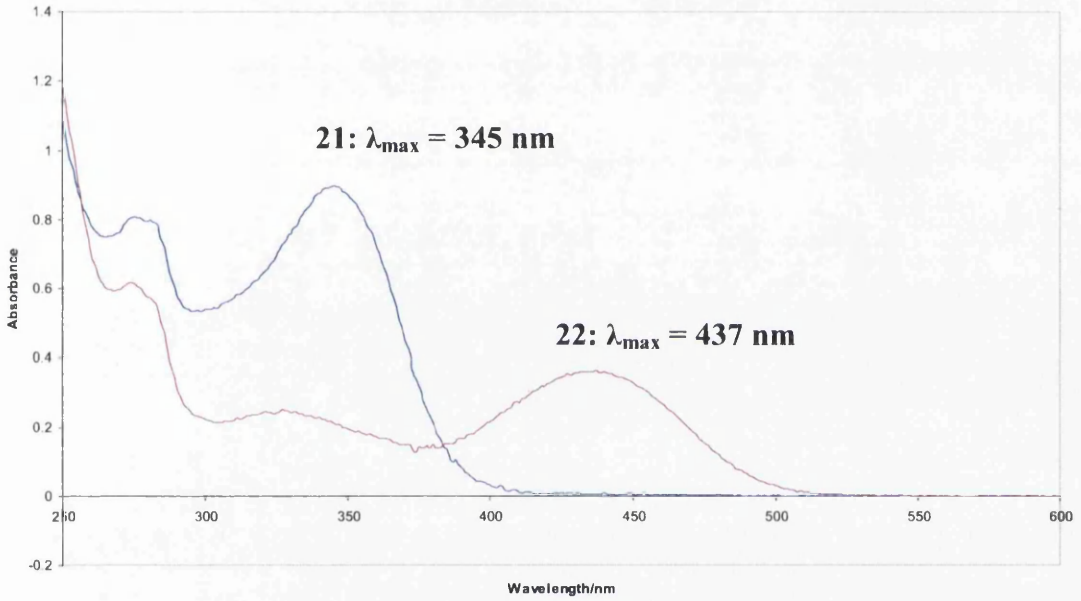


Figure 3.5: The UV-spectral change that accompanies the photochromic conversion of 21 to 22 (cf. Scheme 2.2). The colourless solution of open form 21 (cf. Figure 3.4a) exhibits an absorption at λ = 345 nm. Irradiation with UV light prompts the appearance of a yellow colour (cf. Figure 3.4b), which is accompanied by the reduction of the absorption at λ = 345 nm and the appearance of a new absorption at λ = 437 nm.

The solution retained its yellow colour if left in the dark, but the yellow colour disappeared over the course of an hour in direct sunlight.

3.2.3. *Evaluation of the viability of the proposed donor-acceptor pair.*

As is explained in Section 1.3, the viability of the occurrence of RET for a proposed donor-acceptor pair can be evaluated by the calculation of the Förster distance R_0 from the spectral overlap integral $J(\lambda)$, obtained from spectroscopic measurements. RET can be assumed to occur if the donor-acceptor separation is less than R_0.[4a]

The proposed donor-acceptor distance between the donor *N*-methylacridone (**1**) and the acceptor **22** was worked out in Section 1.3.3 to be 11.3 Å. It follows that if the Förster distance for the proposed donor-acceptor pair **1** and **22** is more than 11.3 Å then the proposed switchable donor-acceptor pair is viable.

N-Methylacridone it is reported in the literature to have an absorption maximum of 256 nm ($\varepsilon = 5.5 \times 10^4$ $dm^3mol^{-1}cm^{-1}$) and an emission maximum of 426 nm ($\Phi_f = 0.89$, $\tau = 11.3$ ns) in methanol.[1] It was necessary to measure the emission spectrum in order to obtain the information for the spectral overlap integral calculation. The emission spectrum of **1** in methanol was measured, which confirmed the literature measurements. The spectrum is shown in **Figure 3.6**.

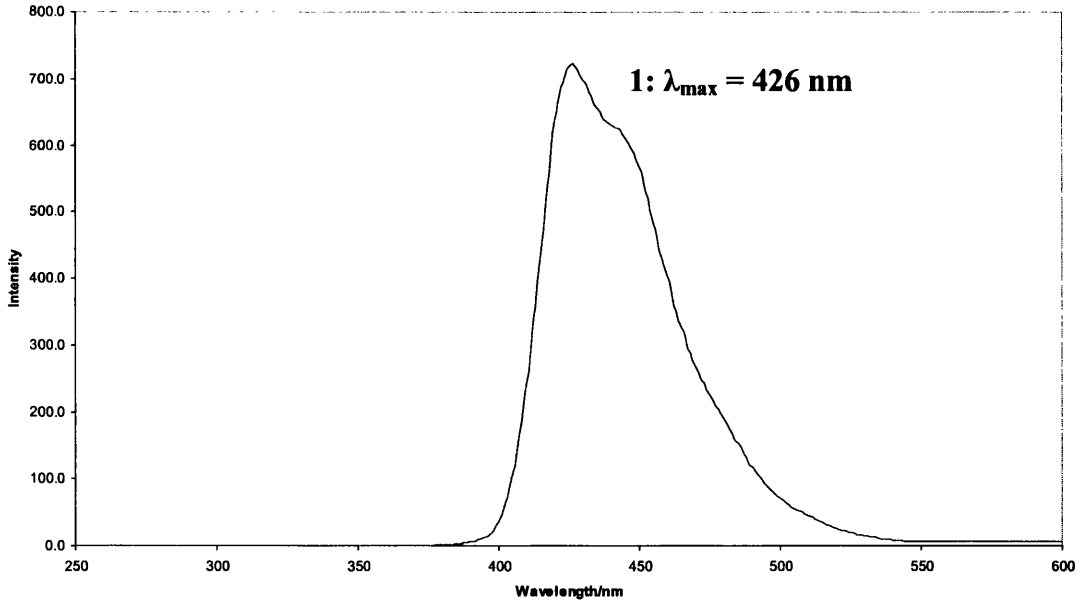


Figure 3.6: The emission spectrum of *N*-methylacridone (1).

The integrated normalised emission spectrum of the donor and the integrated absorption spectrum of the acceptor were used to calculate the spectral overlap integral $J(\lambda)$ using **Equation 1.3** (Chapter 1, Section 1.3.2). A spreadsheet was created containing

the individual emission intensity values at each wavelength in increments of 1 nm, normalised to unity by dividing each value by the sum of all the values. The normalised values of the emission intensity of **1** were multiplied by the extinction coefficients of **22** for each wavelength and by wavelength to the fourth power (λ^4), and the products of this multiplication for each wavelength were added together to give $J(\lambda)$. The value of $J(\lambda)$ was found to be 1.49×10^{14} $dm^3mol^{-1}cm^{-1}nm^4$, which is a typical value of $J(\lambda)$ for viable donor-acceptor pairs.[4a] The spreadsheet used in the calculation is given in the experimental section. The spectral overlap integral is represented in **Figure 3.7** as the overlaid emission spectrum of **1** and absorption spectrum of **22**.

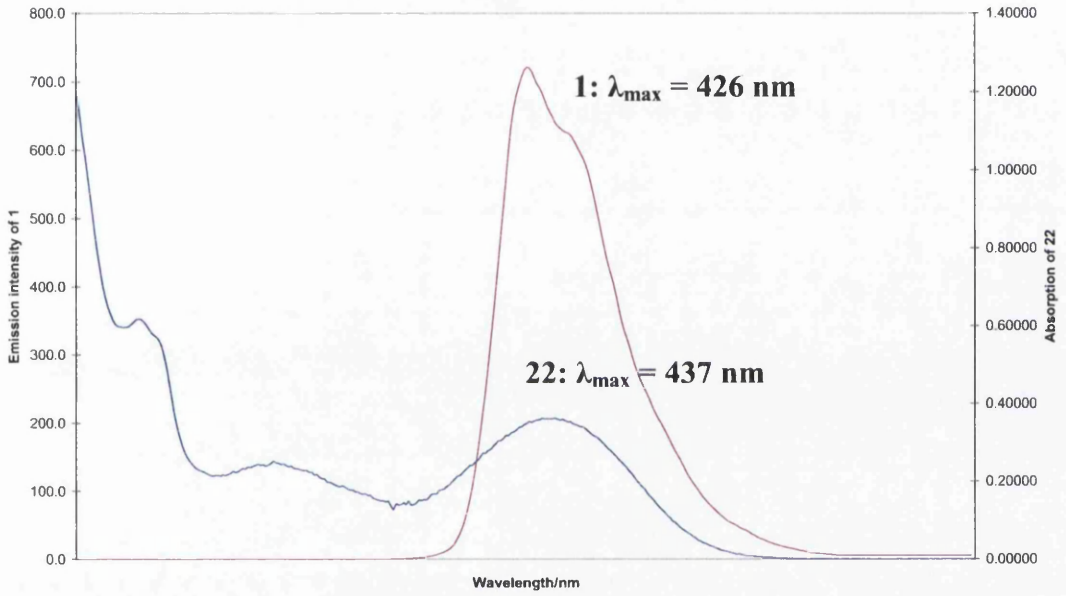


Figure 3.7: The emission spectrum of *N*-methylacridone (1) overlaid with the absorption spectrum of 22 to illustrate the spectral overlap.

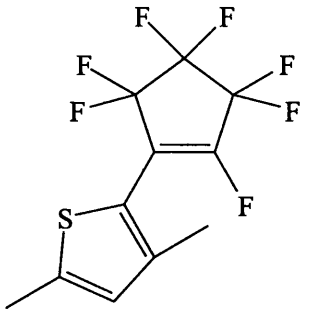
This value of $J(\lambda)$ was used to calculate the Förster distance R_0 using **Equation 1.2** (Chapter 1, Section 1.3.2). Also factored in were the literature fluorescence quantum yield of *N*-methylacridone in methanol (0.89)[1] and the refractive index of methanol (1.328). The value of R_0 was found to be 36.9 Å. (Reference 4*a* contains excellent instructions for the calculation of R_0).

In conclusion, RET can be assumed to occur if the donor-acceptor separation is less than R_0.[4a] The calculated donor-acceptor distance for the planned switchable donor-acccceptor pair is 11.3 Å and R_0 has been experimentally determined to be 36.9 Å. This was considered a very clear indication that the proposed donor-acceptor pair is viable. Therefore the synthesis of the modified linkable photochromic molecule **45** was

undertaken in the hope that, assuming **45** had identical spectroscopic properties to **21** (which would have to be confirmed), switchable RET would occur.

3.3. Synthesis of 1-(3,5-dimethyl-2-thienyl)perfluorocyclopentene (46).

In order to synthesise the asymmetrical linkable photochromic target molecule, it was first necessary to synthesise the monosubstituted compound 1-(3,5-dimethyl-2-thienyl)perfluorocyclopentene (**46**, **Figure 3.8**).

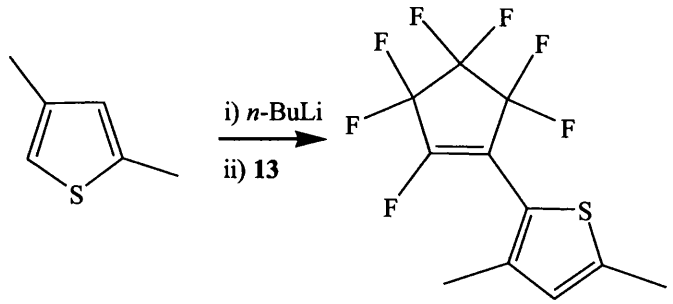


46

Figure 3.8: 1-(3,5-dimethyl-2-thienyl)perfluorocyclopentene (46), the monosubstituted analog of 21 which is needed for the synthesis of the modified target molecule 45.

As discussed in Chapter 1 the synthesis of asymmetrical photochromic diarylperfluorocyclopentenes *via* monosubstituted intermediates such as **46** has been reported (cf. **Scheme 1.8**).[10] Furthermore, the synthesis of **46** was reported by Uchida and Irie, as was the reaction of **46** with a further mole equivalent of lithiated **23** to form **21**.[50] As discussed in Sections 1.11 and 1.12, it was hoped that **46** would react with at least one of several modified disubstituted thiophenes *via* lithiation to form a modified version of **21**, which could then be converted to the linkable target molecule **45**. It was therefore necessary to synthesise **46** from the reaction of **13** with one mole equivalent of lithiated **23**, as shown in **Scheme 3.3**.[50]

The first attempt at this synthesis was carried out in the same way as the synthesis of **21**: Compound **23** was dissolved in THF and lithiated with *n*-BuLi. A solution of compound **13** in THF was then added, and the mixture was warmed to room temperature. The reaction was quenched with HCl and worked up as normal.



23 46

Scheme 3.3: The reaction of 13 with one mole equivalent of 23 *via* lithiation with BuLi to form 46 as reported by Uchida and Irie.[50]

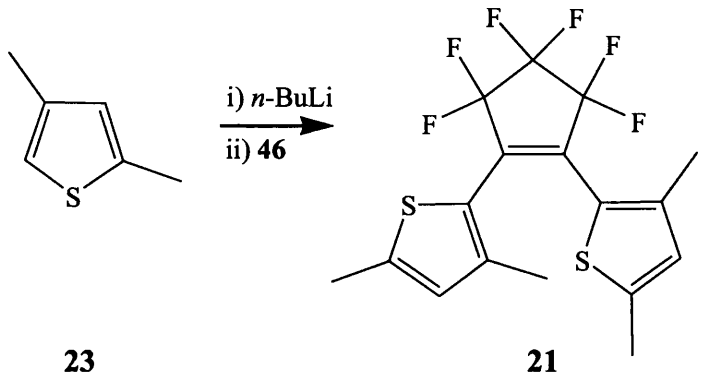
GC analysis of the product mixture showed the disubstituted product **21** and another product. GC:MS analysis revealed that the new product gave a peak at $m/z = 304$, which matched the RMM of the desired product **46**. It was surmised that the reaction had produced a mixture of **21** and **46** as a result of the addition of the solution of **13** to the solution of lithiated **23**. This strategy would naturally result in the formation of **21** due to the resultant abundance of lithiated **23** in the presence of a small amount of **13**, which is known to be susceptible to disubstitution. It was therefore decided to reverse the addition.

The THF solution of lithiated **23** was added to the THF solution of **13**. This had the desired effect on the reaction selectivity and after purification by column chromatography and distillation the product **46** was isolated in 87 %. ^{1}H NMR analysis correlated well with reported values.[50] Analysis by ^{13}C NMR correlated well with predictions and with published data for **13**.[136] ^{19}F NMR analysis correlated well with that of **21**, and correlated well with published data for **13**.[136] High Resolution MS analysis (EI^{+}) showed a peak at $m/z = 304.0149$ which correlates well with the calculated value for the molecular ion of **46**, 304.0151. More detailed characterisation data can be found in the experimental section.

In conclusion, the literature report that **46** can be synthesised conveniently and in high yield by the reaction of one mole equivalent of lithiated **23** with **13** has been confirmed.

3.4. Synthesis of 21 from 46.

As stated previously, an important factor in the planned synthesis is the reported ability of **46** to act as an electrophile in the fluorinated position of the double bond of the perfluorocyclopentene ring. It was considered prudent to test if this was the case by reacting **46** with one further equivalent of lithiated **23**, which had been reported by Uchida and Irie.[50] The reaction is shown in **Scheme 3.4**.



23 **21**

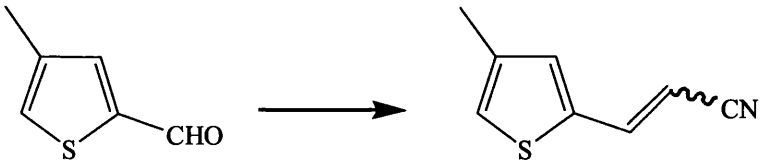
Scheme 3.4: Reaction of lithiated 23 with 46 to form 21, as reported by Uchida and Irie.[50]

Compound **23** was dissolved in THF and lithiated with *n*-BuLi. Compound **46** (1 mol. eq.) was added, and the mixture was warmed to room temperature. The reaction was quenched with HCl and worked up as normal. Purification by column chromatography and recrystallisation afforded **21** in 83 % yield and 96 % purity (GC). The product was identical in all respects to that of the one-step reaction of **23** with **13**.

In conclusion, the literature report that **21** can be synthesised conveniently and in high yield by the reaction of lithiated **23** with **46** has been confirmed. Given this result and the previous reports of the syntheses of non-symmetrical photochromic diarylperfluorocyclopentenes in the literature, it was considered reasonable to assume that **46** would react successfully with other lithiated heterocycles.

3.5 Synthesis of 50 from 51.

The next stage of the planned synthesis, as discussed in Section 1.11.2, involved the synthesis of the novel compound 3-(4-methyl-2-thienyl)acrylonitrile (**50**) from 4-methyl-2-thiophenecarboxaldehyde (**51**) as shown in **Scheme 3.5.**



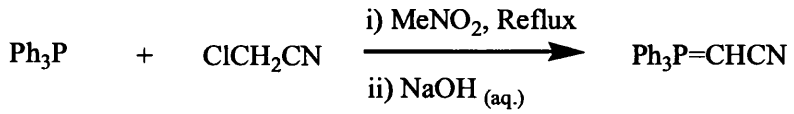
51 **50**

Scheme 3.5: Planned synthesis of 3-(4-methyl-2-thienyl)acrylonitrile (50) from 4-methyl-2-thiophenecarboxaldehyde (51), cf. Section 1.10.2.

Three methods were successfully employed to accomplish this; the Wittig reaction, the Horner/Wadsworth/Emmons reaction and the Knoevenagel-type reaction with cyanoacetic acid in the presence of base. These reactions are discussed below.

3.5.1 Wittig synthesis of 50.

The Wittig reaction, involving the coupling of an aldehyde with a phosphorus ylid, was the first reaction tested. The first step of the reaction was the synthesis of the ylid (triphenyl-λ^5-phosphanylidene)acetonitrile (**52**), as shown in **Scheme 3.6.**



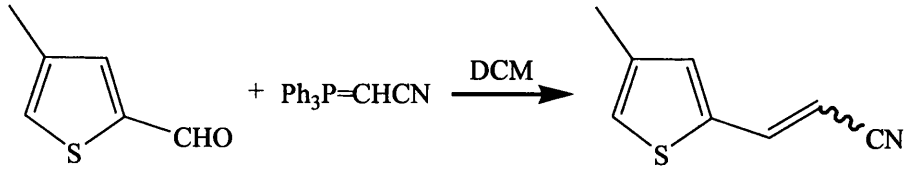
53 **54** **52**

Scheme 3.6: The synthesis of 52 by i) reaction of triphenylphosphine (53) and chloroacetonitrile (54) to form the hydrochloride salt and ii) reaction with NaOH to form 52.

Triphenylphosphine (**53**) and chloroacetonitrile (**54**) were dissolved in nitromethane and refluxed overnight. Upon cooling the hydrochloride salt of **52,** cyanomethylphosphonium chloride, precipitated out. The salt was collected by filtration, washed with Et_2O and isolated in 61 % yield. The salt was then dissolved in distilled

water and treated with aqueous sodium hydroxide solution, at which point **52** precipitated out as white crystals. Extraction with dichloromethane and recrystallisation from Et_2O gave **52** in 52 % overall yield. This was not rigorously characterised but the melting point and ^1H NMR analysis correlated well with published values. The product was immediately used for the synthesis of **50**.

Compounds **51** and **52** were dissolved in dichloromethane and the mixture was refluxed overnight. The reaction is shown in **Scheme 3.7**.



51 **52** **50**

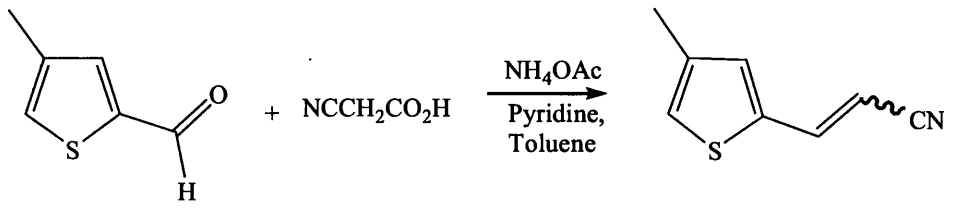
Scheme 3.7: Wittig reaction of 51 with (triphenyl-λ^5-phosphanylidene)acetonitrile (52) to form 50.

After aqueous workup GC analysis showed that the starting material **51** had been consumed and two closely-eluting product peaks in a ratio of approximately 5:1 were present. These were surmised to be the *E*- and *Z*-isomers of **50** respectively. Purification by column chromatography and distillation under reduced pressure yielded **50** as a colourless oil in 88 % yield. ^1H NMR spectroscopy correlated well with predictions and confirmed that the product was a mixture of *E*- and *Z*-isomers of **50**. The olefinic hydrogens α- and β-to the cyano group both gave two sets of doublets corresponding to the different isomers of **50** in a ratio of approximately 5:1. The major doublets had a coupling constant of 16 Hz corresponding to the *E*-isomer and the minor doublets had a coupling constant of 12 Hz corresponding to the *Z*-isomer. ^{13}C NMR analysis showed separate signals for every carbon in each isomer and correlated well with predictions. A nitrile peak was observed in the IR spectrum. High resolution MS analysis (ES^+) showed a peak at m/z = 167.0637 which correlated exactly with the predicted value for the $[M+NH_4]^+$ ion of **50**. More detailed characterisation data can be found in the experimental section.

The reaction of **51** with a sample of **52** which had not been freshly prepared did not lead to the formation of **50**. Mass spectrometric analysis showed that **52** decomposed to form triphenylphosphine oxide over the course of a few weeks.

3.5.2 *Synthesis of **50** via reaction of **51** with cyanoacetic acid.*

The reaction of **51** with cyanoacetic acid (**57**) to form **50** is shown in **Scheme 3.8**.



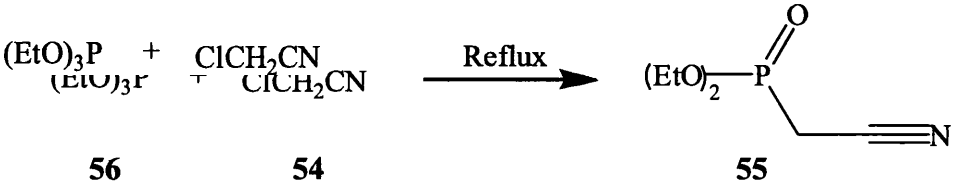
51 **57** **50**

Scheme 3.8: Knoevenagel-type reaction of 51 with cyanoacetic acid (57) in pyridine and toluene and in the presence of ammonium acetate (NH_4OAc) to form 50.

Compounds **51**, **57** and ammonium acetate were dissolved in pyridine and toluene and the mixture was refluxed with a condenser fitted with a Dean & Stark trap for three days. After aqueous workup, GC analysis showed a clean reaction mixture comprised of the two product peaks previously identified as the *E*- and *Z*-isomers of **50** in a ratio of 2.5:1 respectively. Purification by column chromatography and distillation afforded **50** as an light green oil in 84 % yield. The *E*:*Z* isomer ratio, measured by GC and NMR, was approximately 2.5:1 and the sample was identical in all other respects to the product of the Wittig reaction of **51**.

3.5.3 *Horner/Wadsworth/Emmons synthesis of **50**.*

The Horner/Wadsworth/Emmons modification of the Wittig reaction involves the reaction of a carbonyl compound with a phosphonate. The first step in this synthesis was the preparation of the starting material diethylcyanomethylphosphonate (**55**) *via* the neat Arbusov reaction of triethyl phosphite (**56**) with chloroacetonitrile (**54**). This reaction is shown in **Scheme 3.9.**

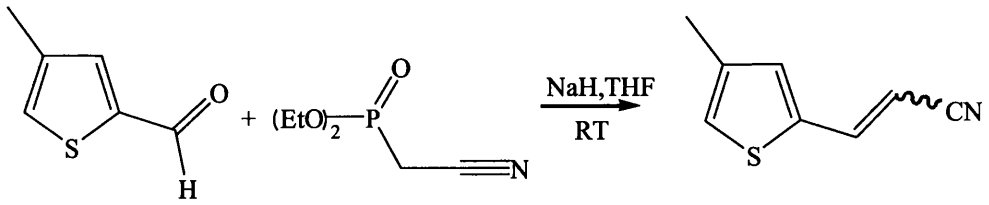


56 **54** **55**

Scheme 3.9: The neat Arbusov reaction of triethyl phosphite (56) with 54 to form 55.

Compound **56** was heated to 100 °C and **54** was added slowly over 15 minutes. The mixture was refluxed for 4 hours, during which time GC analysis showed the gradual consumption of **56** and the emergence of a new peak. After GC analysis showed that **56** had been completely consumed the excess **54** was distilled off under atmospheric pressure. Compound **55** was distilled off under reduced pressure and collected in 81 % yield. The spectra of the product correlated well with predictions and with published data.[98] More detailed characterisation can be found in the experimental section.

The synthesis of **50** *via* the reaction of **51** with **55** is shown in **Scheme 3.10**.



51 **55** **50**

Scheme 3.10: Horner/Wadsworth/Emmons reaction of 51 with diethylcyanomethylphosphonate (55) in the presence of sodium hydride (NaH) to form 50.

Sodium hydride (NaH) was obtained as a 60 % suspension in mineral oil. The NaH was prepared for use by washing a measured amount of this suspension with dry hexane three successive times under an inert atmosphere. The NaH was suspended in dry THF and **55** was added, at which point the suspension darkened and heated up considerably. After stirring for one hour **51** was added and the mixture was stirred overnight. After aqueous workup GC analysis showed that all of the starting material **51** had been consumed and the *E*- and *Z*-isomers of **50** had been produced in a ratio of approximately 5.5:1 respectively. Purification by column chromatography and reduced-pressure distillation afforded 50 as a clear colourless liquid in 91 % yield. Aside from the isomer ratio the product was identical in all respects to the product of the Wittig reaction.

During the course of this work this reaction was repeated several times and gave consistently good yields. The phosphonate starting material **55** did not appear to decompose and was just as effective after several months as when freshly prepared.

3.5.4 *Syntheses of 50: Conclusion.*

The novel compound 3-(4-methyl-2-thienyl)acrylonitrile (**50**) has been synthesised successfully and in high yield by three separate methods. The Wittig reaction was successful but the synthesis of the ylid starting material **52** suffers from certain drawbacks, namely the use of toxic nitromethane for preparation, the low yield of the precipitation of the hydrochloride salt, the high molecular weight leading to the need for large amounts and the decomposition of **52** to form triphenylphosphine oxide.

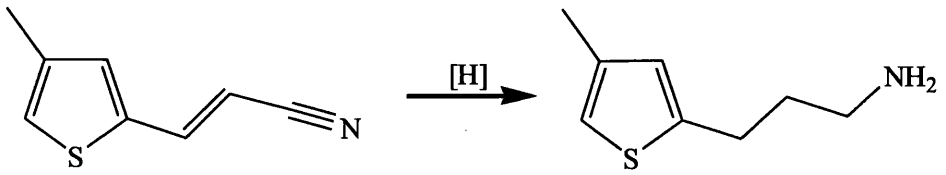
The reaction with cyanoacetic acid was inconvenient due to the toxicity of pyridine and the long reaction times.

The Horner/Wadsworth/Emmons synthesis was the highest yielding reaction. The starting material **55** was easy to prepare and does not appear to decompose appreciably. This reaction was chosen as the most convenient and was repeated later on in the project, although all three reactions were successful and could be used.

3.6 Reduction reactions of cinnamonitrile.

3.6.1 *Introduction*

The next stage in the planned synthesis involved reduction of both the carbon to carbon double bond and the carbon to nitrogen triple bond of **50** to give the desired reduction product 3-(4-methyl-2-thienyl)-1-propylamine (**47**), as shown in **Scheme 3.11.**

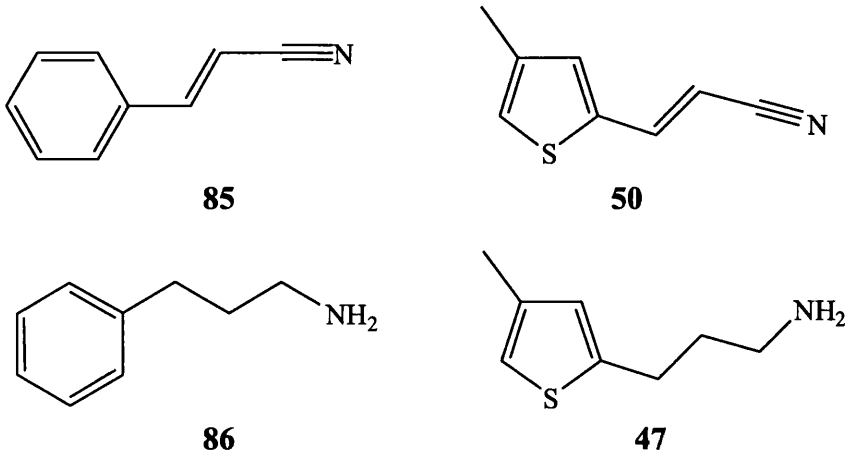


50 **47**

Scheme 3.11: Planned reduction of 50 to give the amine 47.

As **50** is the product of two reaction steps and considerable effort and expense it was thought prudent to conduct initial experiments on a commercially available analogous compound. It was decided to use cinnamonitrile (**85**) due to its similarities in structure, properties and molecular weight to **47**. It was also advantageous that the product of the

analogous desired reduction of cinnamonitrile, 3-phenylpropylamine (**86**) was commercially available. The analogous compounds are shown in **Figure 3.9**.



85 **50**

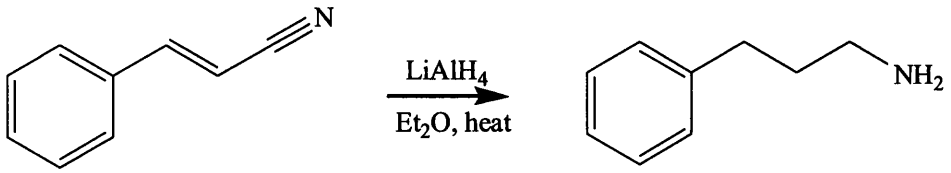
86 **47**

Figure 3.9: The analogous compounds cinnamonitrile (85) and 50, and their analogous reduction products 3-phenyl-1-propylamine (86) and 47.

As discussed in section 1.11.1, literature searching revealed that total reductions of α,β-unsaturated nitriles are rare, but examples of successful reductions have been reported. Several literature methods were applied to the case in question.

3.6.2 Reduction of 85 with lithium aluminium hydride.

Some successful reductions of α,β-unsaturated nitriles with lithium aluminium hydride ($LiAlH_4$) have been reported in the literature. These usually involve the addition of the acrylonitrile to an ether or tetrahydrofuran solution of lithium aluminium hydride followed by refluxing for several hours,[84,85] as shown in **Scheme 3.12**.



85 **86**

Scheme 3.12: Reduction of 85 with lithium aluminium hydride ($LiAlH_4$) in Et_2O to give the amine 86.

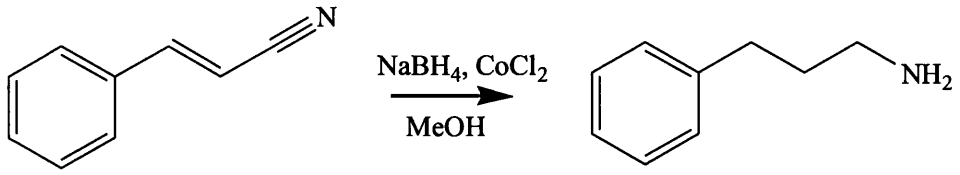
Compound **85** was reacted with lithium aluminium hydride in refluxing Et_2O. Upon aqueous workup the amine was extracted as the hydrochloride salt and GC analysis of the organic phase showed that none of the starting material **85** was present. Basification of

the aqueous phase and evaporation afforded **86** in 35 % yield. Higher yields than this have been reported for this type of reaction,[84] but this is similar to the yield of 42 % reported by Almansa *et al.* in 1996.[85] ^{1}H NMR analysis showed the expected D_2O-exchanging NH_2 signal at $\delta = 1.12$ ppm and the spectrum correlated well with that of an authentic sample of **86**. ^{13}C NMR analysis correlated well with the spectrum of the authentic sample. High-resolution MS analysis (ES^+) showed a peak at m/z = 136.1122 (calculated value of the $[M+H]^+$ ion of **86**; 136.1121). More detailed characterisation data can be found in the experimental section.

The reason for the low yield was unclear as all of the starting material **85** had appeared to be consumed. It could have been due to poor recovery from the acidic workup, so an aliquot of authentic sample of **86** (0.68 g) was dissolved in dichloromethane and extracted as the hydrochloride salt with 2M aqueous HCl. GC analysis of the organic phase showed all the amine had been extracted. The acidic phase was basified with 2M NaOH and extracted with dichloromethane. Upon drying of the organic phase with magnesium sulfate and evaporation **86** was obtained in 94 % recovery (0.64 g). It was not clear why the yield was so low, although it could possibly have been due to the incomplete breakdown of complexes of the amine with aluminium. The reaction was not investigated further as an alternative reaction was available.

3.6.3 *Reduction of **85** with sodium borohydride and cobalt chloride.*

Transition metal catalysts have been widely used in conjunction with reducing agents such as sodium borohydride and lithium aluminium hydride in order to enhance the effectiveness of those reducing agents. As a literature example of the complete reduction of an α,β-unsaturated nitrile to form the appropriate propylamine existed, this was considered a promising route.[86] The literature method involved the reaction of the nitrile with ten equivalents of sodium borohydride and two equivalents of cobalt chloride. It has been reported that the $NaBH_4$ and $CoCl_2$ form the reactive compound cobalt boride (Co_2B) which catalyses the reduction with $NaBH_4$ by forming a complex with the nitrile group and activating it towards reduction by sodium borohydride.[86] The test reduction of **85** is shown in **Scheme 3.13.**



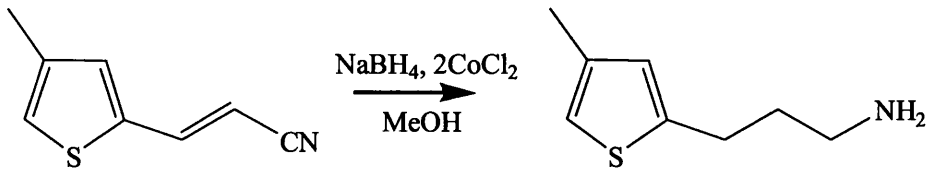
85 **86**

Scheme 3.13: Reduction of 85 with sodium borohydride ($NaBH_4$) and cobalt chloride ($CoCl_2$) in methanol to give the amine 86.

Compound **85** was stirred overnight with $NaBH_4$ and $CoCl_2$ in methanol. Aqueous HCl (4M) was added until the precipitate dissolved, and after extraction with Et_2O the aqueous phase was basified with concentrated ammonia solution (It was necessary to use concentrated ammonia as the use of aqueous NaOH resulted in a thick suspension from which organic solvent would not separate.). The product **86** was extracted with diethyl ether and evaporation afforded **86** in 78 % yield. The purified product was identical to the product of the reduction of **85** with $LiAlH_4$ and the authentic sample of **86**. The yield of this reaction was much better than that of the reduction of **85** with $LiAlH_4$, therefore this reaction was chosen as the best option for the reduction of **50**.

3.7 Reduction of 50 to give 47.

The method used in Section 3.6.3 was applied for the next step in the planned synthesis, the reduction of **50** to **47**. This reaction is shown in **Scheme 3.14**.



50 **47**

Scheme 3.14: Reduction of 50 with $NaBH_4$ and $CoCl_2$ in methanol to give the amine 47.

The reaction was carried out in exactly the same fashion as the reduction of **85** and **47** was successfully obtained in 63 % yield. The yield was lower than that of **86**, but was adequate for the continuation of the project. ^1H NMR analysis of **47** showed the expected D_2O-exchanging NH_2 signal at $\delta = 1.12$ ppm and the spectrum correlated well with predictions. ^{13}C NMR analysis correlated well with predictions. High-resolution MS analysis (ES^+) showed a peak at $m/z = 156.0843$ (calculated value for the $[M+H]^+$ ion of

47; 156.0841). More detailed characterisation information can be found in the experimental section. This reaction was repeated several times during the course of this project and at different scales. It was found that the yields were generally consistent.

In conclusion, the novel compound **47** was successfully synthesised by the reduction of **50** with sodium borohydride and cobalt chloride in methanol.

3.8 Amine protection reactions.

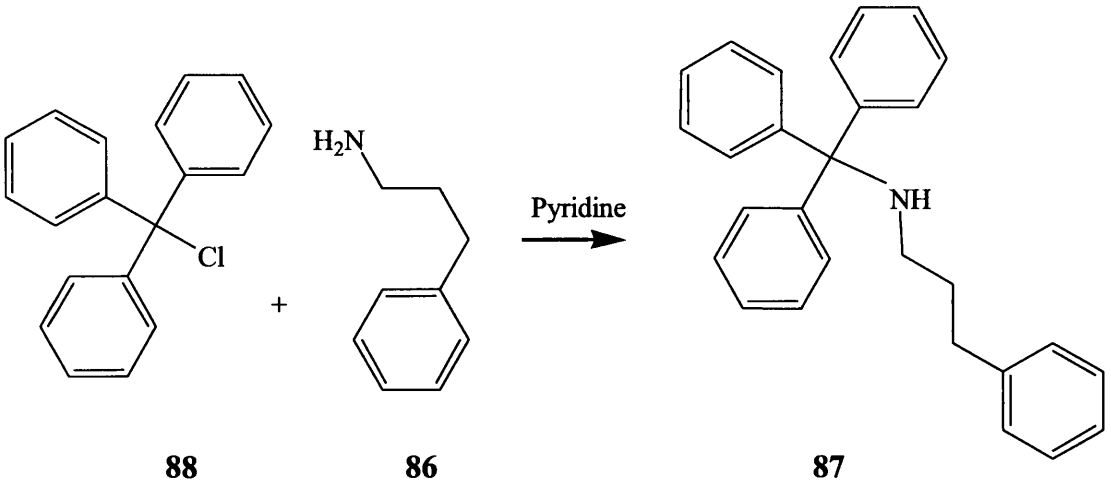
3.8.1 Introduction

As discussed in Section 1.11.3, it was thought necessary to protect the amino functionality of **47** with a base stable protecting group before the final lithiation reaction with **46** to form the target molecule **45**. The protecting groups that were chosen were the triphenylmethyl (trityl) group (introduced by the reaction of an amine with trityl chloride), the 4,4',4''-trimethoxytrityl (TMT) group (introduced by the reaction of an amine with 4,4',4''-trimethoxytrityl tetrafluoroborate, $TMTBF_4$) and the Boc group (introduced by the reaction of an amine with Boc anhydride). Again, as the amine **47** was the product of several synthetic steps it was decided that initial test protection reactions would first be carried out on **86** before **47** was used. The test protection reactions of **86** and the protection reactions of **47** are discussed below.

*3.8.2 Trityl protection of **86**.*

As there was some indication in the literature that the trityl group was stable to organolithium reagents,[102,103] this group was selected as a potential protecting group. Compound **86** was protected as the trityl derivative *N*-(3-phenyl-1-propyl)tritylamine (**87**), which to the best of the author's knowledge is a novel compound, by reaction with trityl chloride (**88**) in pyridine. The reaction is shown in **Scheme 3.15**.

Addition of water caused a white solid to precipitate out. Purification of the solid by column chromatography and recrystallisation afforded **87** as white crystals in 53 % yield. This yield is similar to those reported in the literature for this type of reaction.[105,106]



88 **86** **87**

Scheme 3.15: Test protection of 86 as the trityl derivative 87 by reaction with trityl chloride (88) in pyridine.

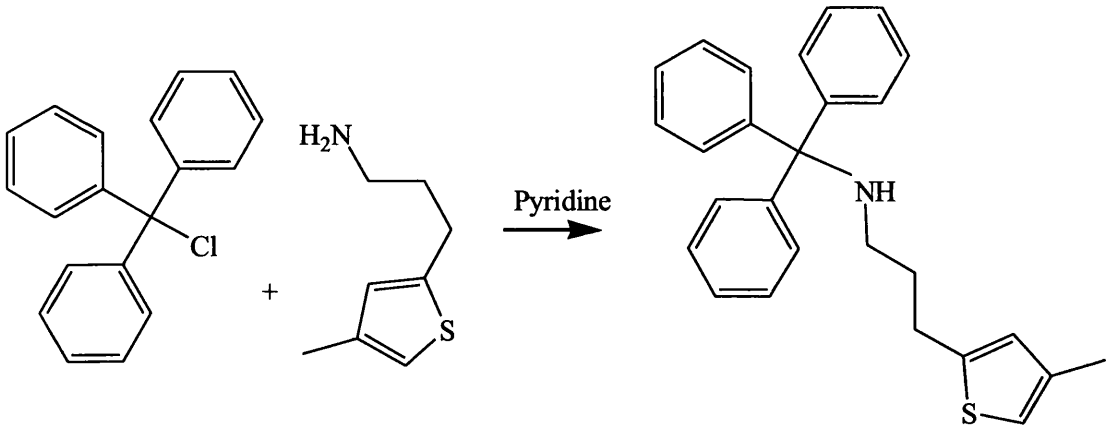
^{1}H NMR analysis showed the expected D_2O-exchanging NH signal at δ = 1.45 ppm. The signal corresponding to the CH_2 positioned α-to the NH group had been shifted upfield and had lost some fine structure in comparison to the analogous signal in the spectrum of compound **86**. ^{13}C NMR and microanalysis data correlated well with predictions. High-resolution MS analysis (ES^+) showed a peak at *m/z* = 378.2217 (predicted value for the protonated form of **87**; 378.2216). More detailed experimental data can be found in the experimental section.

In conclusion, the novel compound **87** was synthesised successfully by the reaction of **86** with **88**.

3.8.3 Trityl protection of 47.

The protection reaction of **47** with **88** to form the novel compound *N*-[3-(4-methyl-2-thienyl)-1-propyl]tritylamine (**60**) is shown in **Scheme 3.16**.

The reaction was carried out in exactly the same fashion as the synthesis of **87**, and **60** was obtained as white crystals in 54 % yield. This yield was surprisingly similar to the yield of the synthesis of **87** and was, again, comparable to literature values for analogous compounds.[105,106]



88 **47** **60**

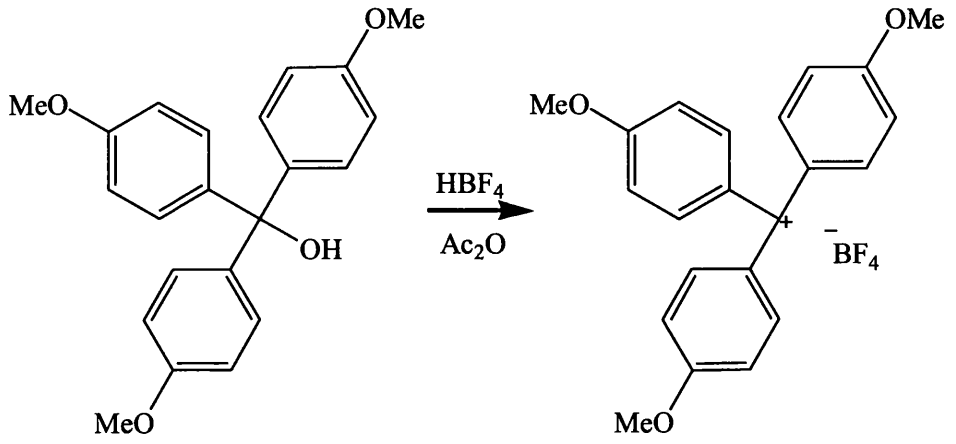
Scheme 3.16: Protection of 47 as the trityl derivative 60 by reaction with 88 in pyridine.

^{1}H NMR analysis showed the expected D_2O-exchanging NH signal at δ = 1.45 ppm and the signal corresponding to the CH_2 α-to the NH group showed a similar upfield shift and loss of fine structure in comparison to **47** as was observed in the spectrum of **87**. ^{13}C NMR analysis and microanalysis data correlated well with predictions. High-resolution MS analysis (ES^+) showed a peak at *m/z* = 398.1936 (predicted value for the protonated form of **47**; 398.1937). More detailed characterisation data can be found in the experimental section.

In conclusion, the novel compound **60**, which is the trityl-protected derivative of **47** was successfully synthesised by the reaction of **47** with **88**. The results of the lithiation reactions of **60** are reported in Section 3.9.

3.8.4 Synthesis of 4,4',4''-trimethoxytrityl tetrafluoroborate (90).

As discussed in section 1.11.3, methoxytrityl groups are reportedly easier to remove than the parent trityl group. The best reported way in which to protect amines with this group is to react the amine with 4,4',4''-trimethoxytrityl tetrafluoroborate (**90**), synthesised from the reaction of commercially available 4,4',4''-trimethoxytrityl alcohol (**89**) and aqueous fluoroboric acid.[107,108] This reaction is shown in **Scheme 3.17**.



89 **90**

Scheme 3.17: Reaction of 4,4',4''-trimethoxytrityl alcohol (89) with fluoroboric acid (HBF_4) in acetic anhydride (Ac_2O)

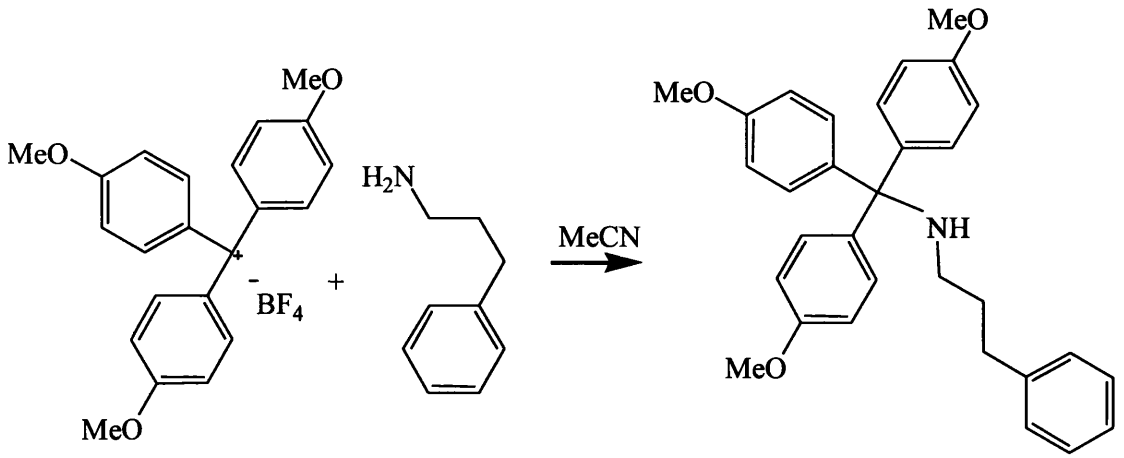
Slow addition of fluoroboric acid to the clear colourless acetic anhydride solution of **89** produced a purple solution. After stirring for 2 hours, diethyl ether (in which **89** is soluble but **90** is not) was added to the solution and over the next hour **90** precipitated out as purple crystals. Compound **90** was collected by Büchner filtration in 94 % yield. Melting point and ^1H NMR analyses correlated well with literature values.[108] ^{13}C NMR analysis correlated well with predictions. High-resolution MS analysis (ES^+) showed a peak at m/z = 333.1486 (predicted value for the trimethoxytrityl cation; 333.1485). More detailed characterisation data can be found in the experimental section.

*3.8.5 TMT Protection of **86**.*

Compound **86** was protected as the trityl derivative *N*-(3-phenyl-propyl)-4,4',4''-trimethoxytritylamine (**91**), which to the best of the author's knowledge is a novel compound, by reaction with **90** in acetonitrile. The reaction is shown in **Scheme 3.18**.

This reaction consisted of slow dropwise addition of **86** to a purple solution of **90** in dry acetonitrile. Upon addition, according to literature procedures, of two mole equivalents of the amine[108] the purple solution turned light green and was stirred for one hour. The solution was evaporated, aqueous sodium hydroxide (2M) was added to destroy the fluoroboric acid produced by the reaction, and the aqueous phase was extracted with

diethyl ether. Purification by column chromatography afforded the protected amine **91** in 54% yield as an off-white gum.



90 **86** **91**

Scheme 3.18: Protection of 86 as the TMT derivative 91 by reaction with 90 in acetonitrile.

^{1}H NMR analysis showed the expected three CH_2 signals, but the quintet corresponding to the CH_2 group β-to the NH gave an integration of 3H. Upon reaction with D_2O the integration of this signal became equal to that of the other two CH_2 signals. It was concluded that the NH signal was present but was overlaid by the CH_2 signal. The CH_2 signal α-to the NH showed an upfield shift in comparison to the analogous signal in the spectrum of **86**, but there was no loss of fine structure as was observed in the spectra of the trityl-protected amines **87** and **60**. ^{13}C NMR analysis correlated well with predictions. High-resolution MS analysis (EI^+) showed a peak at m/z = 467.2448 (calculated mass of the molecular ion; 467.2455).

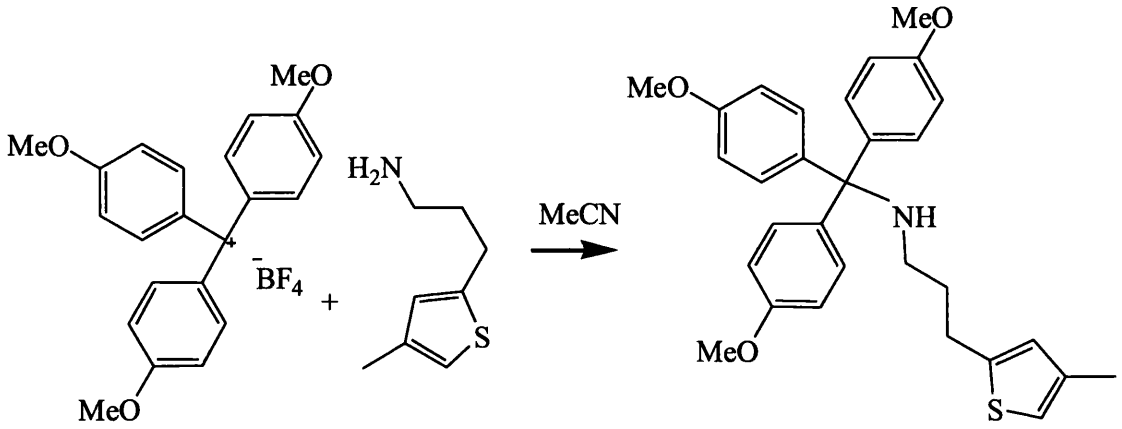
The yield of the reaction was 54 %. Literature yields for this type of reaction range from 44 % to 69 %,[108] so this yield was unsurprising. As two equivalents of the amine **86** were used in the reaction, following literature procedure, the yield relative to the amine works out as 27 %, which was thought to be unfortunately low. When one equivalent of **86** was used there was no evidence of formation of the product **91**. All the yields of the trityl and TMT-protection reactions are very similar, which suggested that the reactions exist as equilibria. The known fact that the TMT group is easier to remove than the trityl group suggested that in such an equilibrium the TMT-protected amine would be less favoured than the analogous trityl-protected amine, hence the need for twice as much amine in the reaction to produce the same amount of product. It was surmised that the fluoroboric acid or HCl (in the case of the reaction with trityl chloride) produced in the

reaction could deprotect the trityl derivatives and lower the yield, but the trityl-protection reaction was carried out in pyridine which should have served to remove the HCl from the reaction mixture, and the yields were still low. This was not investigated, however, as the amount of protected amines produced were sufficient for the next stages of the project.

In conclusion, the novel compound **91** was successfully synthesised by the reaction of **86** with **90**. Although the yield was low the fact that the product was successfully synthesised led to the reaction being considered a successful test, and the protection reaction of **47** was carried out.

3.8.6 TMT protection of 47.

The protection reaction of **47** with **90** to form the novel compound *N*-[3-(4-methyl-2-thienyl)-1-propyl]-4,4',4''-trimethoxytritylamine (**61**) is shown in **Scheme 3.19**. The reaction was conducted in the same fashion as the synthesis of **91** and the product **61** was isolated as an off-white gum in 55 % yield. This is again calculated in relation to **90** and works out as 28 % yield in relation to the amount of **47** used. This was expected, as discussed in the preceding section.



90 **47** **61**

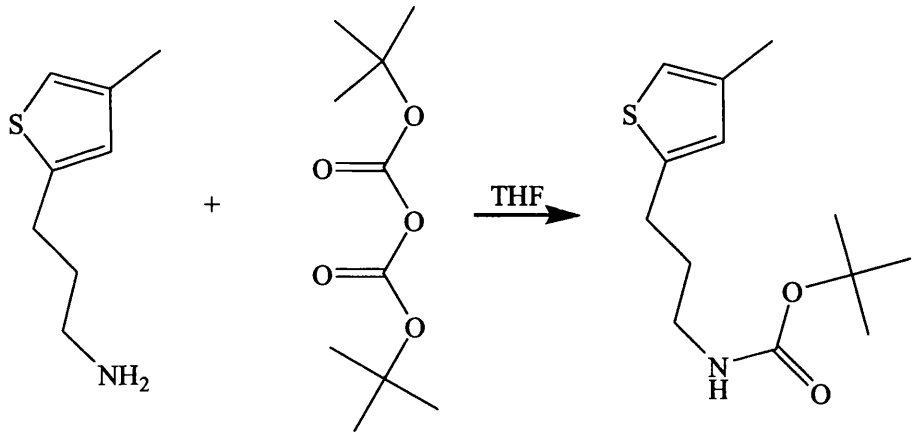
Scheme 3.19: Protection of 47 as the TMT derivative 61 by reaction with 90 in acetonitrile.

^{1}H NMR analysis showed that the CH_2 group α- to the NH had shifted upfield and was overlaid with the thienyl CH_3 signal and the NH signal, which was again concluded from the change in integration upon D_2O exchange. ^{13}C NMR analysis correlated well with predictions. High-resolution MS analysis showed a peak at m/z = 486.2088 (predicted value for the $[M-H]^+$ ion of **61**, 486.2097. More detailed characterisation data can be found in the experimental section

In conclusion, the novel compound **61**, which is the TMT-protected derivative of **47,** was successfully synthesised by the reaction of **47** with **90**. The results of the lithiation reactions of **61** are reported in Section 3.9.

3.8.7 Boc protection of 47.

The test reaction of **86** with Boc anhydride was not carried out due to assurances from colleagues that the Boc-protection reaction would not be problematic. Compound **47** was stirred overnight with Boc anhydride (**62**) in THF under an inert atmosphere. Aqueous workup and purification by column chromatography afforded [3-(4-methyl-2-thienyl)-1-propyl]carbamic acid tert-butyl ester (**63**) as an light green oil in 93 % yield. The reaction is shown in **Scheme 3.20**.



47 **62** **63**

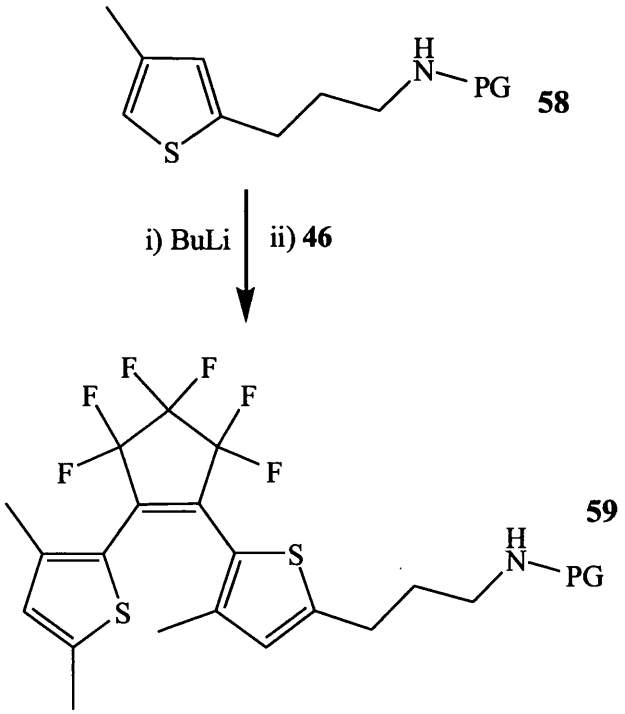
Scheme 3.20: Protection of 47 as the Boc derivative 63 by reaction with 62 in THF.

^{1}H NMR analysis showed the expected D_2O-exchanging NH signal at $\delta = 4.51$ ppm, and the signal corresponding to the CH_2 group α-to the NH showed a loss of fine structure and a downfield shift in comparison with the analogous signal in the spectrum of **47**. This is in contrast to the upfield shift observed by the same group in the TMT and trityl-protected amines. The spectrum correlated well with predictions. ^{13}C NMR analysis correlated well with predictions. The expected carbonyl peak was evident in the IR spectrum. High-resolution MS analysis (ES^+) showed a peak at $m/z = 256.1367$ (calculated value for the protonated form of **63**; 256.1366). More detailed characterisation data can be found in the experimental section.

In conclusion, the novel compound **63**, which is the Boc-protected derivative of **47,** was successfully synthesised by the reaction of **47** with **62**. The results of the lithiation reactions of **62** are reported in Section 3.9.

3.9 Lithiation of protected amines and attempted reaction with 46.

As discussed in Section 1.11.3, the next stage of this work involved the lithiation of the protected amines (represented by the generic structure **58**) and reaction with the monothienyl compound **46** in the hope that substitution would take place on the thiophene ring of the protected amine, in a similar fashion to the reaction of **46** with **23**. If everything went according to plan this reaction would produce a protected derivative of the target molecule **45** (represented by the generic structure **59**). This proposed reaction is shown in **Scheme 3.21**.



Scheme 3.21: Proposed lithiation of 58 (47 protected with PG, a base-stable protecting group) and reaction with 46 to form 59, a protected version of 45.

The reaction shown in **Scheme 3.21** was attempted using all three protected amines **60**, **61** and **63** as the starting material (represented in **Scheme 3.21** by structure **58**) using one mole equivalent of BuLi and one equivalent of **46**. The lithiations of the protected amine were carried out at 0 °C for one hour. Compound **46** was added and the mixture

was stirred overnight. The reactions were quenched with saturated aqueous ammonium chloride solution and worked up in the usual way. In each case, TLC, NMR and GC-MS analysis showed a mixture of products. There was little indication that the desired products had formed, which could have been due to the decomposition of the products during the analysis. Regardless, these indications were not promising. Attempts to separate the mixtures with column chromatography (using neutral alumina as the solid phase) were fruitless. Although all of the chromatographed material was recovered, fractions that appeared to be pure upon analysis of the separated products by TLC appeared to be mixtures of components in varying ratios when analysed by other techniques. In any case, none of the fractions when weighed corresponded to a good or even acceptable yield of product. It was speculated that the proton of the NH group could be removed by the organolithium reagent in spite of the presence of the protecting group, and perhaps the use of a second mole equivalent of BuLi would result in deprotonation of the thiophene ring and the formation of the desired product.

The reactions were attempted again, this time using two mole equivalents of BuLi instead of one. The results of the reactions were the same as previously reported. Analysis of the product mixture by several techniques revealed many products, chromatographic separation was ineffective and gave no fraction in useful yields, and there was no indication that the desired products were present.

The reasons for the lack of success of these reactions were never satisfactorily confirmed. The sulfur heteroatom of the thiophene ring is known to have a powerful directing effect to the α-position, and it was hoped that this would overcome other possible drawbacks in this reaction. All the protected amines contain sites that could be attacked by BuLi. Examples include the NH proton and the CH_2 group α-to the NH of all of the substrates, the ring protons of the anisyl groups of **61** and the carbonyl group of **63**. The lack of one definite major product of these reactions suggests that no one reaction predominates. No product was isolated and characterised satisfactorily, so this can only be speculation.

The protected amines were only ever obtained in small amounts and with the exception of the Boc-protected amine **63** the yields of the protection reactions were low. In order to investigate these reactions further it would have been necessary to synthesise more of the protected amines which were the end products of several synthetic steps. The amount of synthetic work required to synthesise larger batches of protected amines combined with the lack of encouraging results of the protected amine reactions led to this

synthetic route being discounted as a possible avenue for the synthesis of **45**. Another route which, it was hoped, would not suffer from the same drawbacks as this one was pursued. The results of this work are reported in Chapter 4.

3.10 Conclusion to Chapter 3.

The photochromic molecule 1,2-*bis*(3,5-dimethyl-2-thienyl)perfluorocyclopentene (**21**) has been successfully synthesised by reacting lithiated 2,4-dimethylthiophene (**23**) with 0.5 mole equivalents of octafluorocyclopentene (**13**), as has been reported in the literature.[50] Compound **21** has been shown to be photochemically converted to the closed form **22**, as has been reported in the literature.[50]

The spectral overlap integral ($J(\lambda)$) of the emission spectrum of *N*-methylacridone (**1**) with the absorption spectrum of **22** was found to be 1.49×10^{14} $dm^3mol^{-1}cm^{-1}nm^4$. The Förster distance was calculated to be 36.9 Å, which confirmed that if **1** and **22** were linked together with a donor-acceptor distance of 11.3 Å then RET could be assumed to occur.[4a]

It has been confirmed that the monosubstituted perfluorocyclopentene **46** can be synthesised by the reaction of **23** with one mole equivalent of **13**, and that **46** can react with a further equivalent of lithiated **23** to form **21**. This has been previously reported in the literature,[50] but was important to confirm as the later stages of the project involved the reaction of **46** with other lithiated heterocycles.

The novel compound 3-(4-methyl-2-thienyl)acrylonitrile (**50**) has been synthesised successfully by three different routes from the starting material 4-methyl-2-thiophenecarboxaldehyde (**51**), and has been successfully reduced to the novel compound 3-(4-methyl-2-thienyl)-1-propylamine (**47**). Test reductions of cinnamonitrile (**85**) were also carried out successfully.

Compound **47** has been successfully protected as the triphenylmethyl (trityl), 4,4',4''-trimethoxytrityl (TMT) and *tert*-butoxycarbonyl (Boc) derivatives (**60**, **61** and **63** respectively), all of which are novel compounds. In the case of the trityl and TMT derivatives, test protections of 3-phenyl-1-propylamine (**86**) were also carried out successfully to afford novel compounds.

The reactions of **60**, **61** and **63** with **46** *via* lithiation in an attempt to synthesise a protected derivative of the linkable photochromic target **45** were all unsuccessful, and no products were isolated or characterised.

The synthesis of **45** *via* the protected forms of the amine **47** has therefore been shown not to be viable and can be discounted as a possible synthetic route. However, while the ultimate aim of this chapter was not achieved, several novel compounds were successfully synthesised. Furthermore, the reactions studied in this chapter would go on to become useful in the subsequent work towards the goal of this project, which is reported in Chapter 4.

3.11 Experimental.

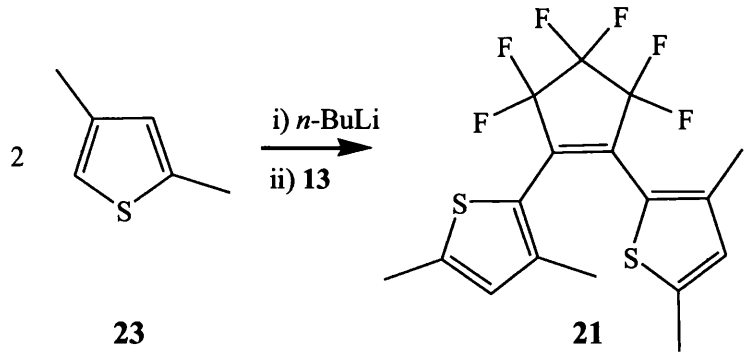
3.11.1 General Experimental

See Chapter 2 Section 2.6.1.

3.11.2 GC Conditions.

Instrument	Hewlett Packard HP5890 Series II
	Gas Chromatograph with HP3396 Series II integrator.
Column	Zorbax ZB-5 5 % Phenyl 95 % Dimethylpolysiloxane
	30 m length 0.32 mm i.d.
Injection Mode	Splitless. Purge on at 0.7 minutes.
Injection Volume	0.5 µL
Injector Temperature	300 °C
Detector Temperature	300 °C
Temperature Programme	60 °C for 0 minutes
	Ramp A 3 °C/min to 95 °C. Hold for 0 minutes
	Ramp B 5 °C/min to 200 °C. Hold for 5 minutes.
	Ramp C 5 °C/min to 340 °C. Hold for 15 minutes.
Detector Attenuation	0
Detector Range	4
Integrator Attenuation	10
Integrator Chart Speed	0.2 cm/min
Integrator Area Rejection	50 1/8 µV-sec
Integrator Threshold	11
Integrator Peak Width	0.04 min

3.11.3 Synthesis of 1,2-bis(3,5-dimethyl-2-thienyl)-perfluorocyclopentene (21).



23 **21**

Scheme 3.22: The reaction of 13 with 2 mole equivalents of 23 *via* lithiation with BuLi to yield the photochromic molecule 21 as reported by Uchida and Irie in 1995.[50]

2,4-Dimethylthiophene (**23**, 2.35 g, 20.9 mmol) was dissolved in dry distilled tetrahydrofuran (40 mL) in a 250 mL round-bottomed flask that had been dried in an oven overnight and flushed with argon. This colourless solution was cooled in ice/water. Butyllithium (8.5 mL of a 2.5 mol dm^{-3} solution in pentane, 20.9 mmol) was added dropwise to the reaction vessel. The resulting bright yellow solution was stirred for 90 min and then cooled to -30 °C. Octafluorocyclopentene (**13**, 2.22 g, 10.5 mmol collected in an ice-cooled trap and dissolved in 10 mL THF) was added dropwise *via* syringe over 5 min. The reaction mixture turned dark blue. The solution was stirred for 1 hour and allowed to warm to room temperature. Aqueous hydrochloric acid (2M, 100 mL) was added to the mixture. The mixture was extracted with diethyl ether (3 x 120 mL). The organic phase was washed with saturated aqueous sodium chloride solution and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was purified by silica gel chromatography (hexane) and recrystallisation (hexane). The expected product **21** was isolated as bright yellow crystals (mp 128.9-130.2 °C, lit.[50] 130 °C) in 78 % yield (3.23 g, 8.12 mmol) and 96.5 % purity (GC). λ_{max} (MeOH)/nm 345 (ε/$dm^3mol^{-1}cm^{-1}$ 1.18 x 10^4). After irradiation with light at 366 nm for 15 minutes: 437 (4.5 x 10^3). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.67 (6H, s, CH_3), 2.38 (6H, s, CH_3), 6.44 (2H, s, C*H*). δ_C (100 MHz; $CDCl_3$; Me_4Si) 15.6, 15.7 (2 x CH_3), 111.3 (tm, $^1J_{C\text{-}F}$ = 268 Hz, perfluorocyclopentenyl 4-*C*), 116.3 (tm, $^1J_{C\text{-}F}$ = 257 Hz, perfluorocyclopentenyl 3-*C*, 5-*C*), 121.3 (thienyl 2-*C*), 129.7 (thienyl 4-*C*H), 134.0 (m, perfluorocyclopentenyl 1-*C* + 2-*C*), 141.7 (thienyl 3-*C*), 144.5 (thienyl 5-*C*). δ_F (376 MHz, $CDCl_3$) -131.2 (4-*F*), -109.1 (3-*F* + 5-*F*). *m/z* (EI^+) = 396.0436 ($[M]^+$ $C_{17}H_{14}F_6S_2$ requires

396.0436). *m/z* (EI^+) = 396 ($[M]^+$ 82 %), 381 ($[M\text{-}CH_3]^+$ 19%), 347 (25 %), 110 (23 %), 59 (100 %). *m/z* ($CI^+(NH_3)$) 296 ($[M]^+$ 12 %), 377 ($[M\text{-}F]^+$ 100 %), 52 (77 %).

3.11.4 *Spreadsheet for the calculation of the spectral overlap integral of 1 and 22.*

λ/ nm	NMA emission intensity	Emission Intensity/ sum of intensities B/38837.6903	Absorbance of B-Form of original molecule	ε/ $Dm^3mol^{-1}cm^{-1}$ D/0.0000732	Wavelength[4] nm^4 A^4		J C*E*F
250	0.0	1.96E-14	1.18995	1.63E+04	3.91E+09		1.24E+00
251	0.0	2.31E-14	1.13819	1.55E+04	3.97E+09		1.42E+00
252	0.0	2.71E-14	1.08170	1.48E+04	4.03E+09		1.62E+00
253	0.0	3.19E-14	1.03228	1.41E+04	4.10E+09		1.84E+00
254	0.0	3.75E-14	0.98124	1.34E+04	4.16E+09		2.10E+00
255	0.0	4.42E-14	0.92939	1.27E+04	4.23E+09		2.37E+00
256	0.0	5.20E-14	0.87598	1.20E+04	4.29E+09		2.67E+00
257	0.0	6.11E-14	0.82874	1.13E+04	4.36E+09		3.02E+00
258	0.0	7.19E-14	0.78350	1.07E+04	4.43E+09		3.41E+00
259	0.0	8.46E-14	0.74444	1.02E+04	4.50E+09		3.87E+00
260	0.0	9.96E-14	0.70425	9.62E+03	4.57E+09		4.38E+00
261	0.0	1.17E-13	0.67461	9.22E+03	4.64E+09		5.01E+00
262	0.0	1.38E-13	0.64681	8.84E+03	4.71E+09		5.74E+00
263	0.0	1.62E-13	0.62897	8.59E+03	4.78E+09		6.66E+00
264	0.0	1.91E-13	0.61507	8.40E+03	4.86E+09		7.78E+00
265	0.0	2.24E-13	0.60379	8.25E+03	4.93E+09		9.13E+00
266	0.0	2.64E-13	0.59797	8.17E+03	5.01E+09		1.08E+01
267	0.0	3.11E-13	0.59690	8.15E+03	5.08E+09		1.29E+01
268	0.0	3.65E-13	0.59511	8.13E+03	5.16E+09		1.53E+01
269	0.0	4.30E-13	0.59580	8.14E+03	5.24E+09		1.83E+01
270	0.0	5.06E-13	0.59688	8.15E+03	5.31E+09		2.19E+01
271	0.0	5.95E-13	0.60356	8.25E+03	5.39E+09		2.65E+01
272	0.0	7.00E-13	0.60933	8.32E+03	5.47E+09		3.19E+01
273	0.0	8.23E-13	0.61534	8.41E+03	5.55E+09		3.84E+01
274	0.0	9.69E-13	0.61811	8.44E+03	5.64E+09		4.61E+01
275	0.0	1.14E-12	0.61631	8.42E+03	5.72E+09		5.49E+01
276	0.0	1.34E-12	0.61083	8.34E+03	5.80E+09		6.49E+01
277	0.0	1.58E-12	0.60271	8.23E+03	5.89E+09		7.65E+01
278	0.0	1.86E-12	0.59180	8.08E+03	5.97E+09		8.96E+01
279	0.0	2.18E-12	0.58169	7.95E+03	6.06E+09		1.05E+02
280	0.0	2.57E-12	0.57533	7.86E+03	6.15E+09		1.24E+02
281	0.0	3.02E-12	0.57067	7.80E+03	6.23E+09		1.47E+02
282	0.0	3.56E-12	0.56270	7.69E+03	6.32E+09		1.73E+02
283	0.0	4.18E-12	0.54779	7.48E+03	6.41E+09		2.01E+02
284	0.0	4.92E-12	0.52111	7.12E+03	6.51E+09		2.28E+02
285	0.0	5.79E-12	0.48859	6.67E+03	6.60E+09		2.55E+02
286	0.0	6.81E-12	0.44804	6.12E+03	6.69E+09		2.79E+02
287	0.0	8.01E-12	0.40896	5.59E+03	6.78E+09		3.04E+02
288	0.0	9.43E-12	0.37262	5.09E+03	6.88E+09		3.30E+02
289	0.0	1.11E-11	0.34033	4.65E+03	6.98E+09		3.60E+02
290	0.0	1.30E-11	0.31466	4.30E+03	7.07E+09		3.97E+02

291	0.0	1.53E-11	0.29265	4.00E+03	7.17E+09	4.40E+02
292	0.0	1.81E-11	0.27485	3.75E+03	7.27E+09	4.93E+02
293	0.0	2.12E-11	0.26126	3.57E+03	7.37E+09	5.59E+02
294	0.0	2.50E-11	0.25206	3.44E+03	7.47E+09	6.43E+02
295	0.0	2.94E-11	0.24389	3.33E+03	7.57E+09	7.42E+02
296	0.0	3.46E-11	0.23589	3.22E+03	7.68E+09	8.56E+02
297	0.0	4.07E-11	0.23139	3.16E+03	7.78E+09	1.00E+03
298	0.0	4.79E-11	0.22819	3.12E+03	7.89E+09	1.18E+03
299	0.0	5.63E-11	0.22590	3.09E+03	7.99E+09	1.39E+03
300	0.0	6.63E-11	0.22196	3.03E+03	8.10E+09	1.63E+03
301	0.0	7.80E-11	0.21868	2.99E+03	8.21E+09	1.91E+03
302	0.0	9.17E-11	0.21564	2.95E+03	8.32E+09	2.25E+03
303	0.0	1.08E-10	0.21466	2.93E+03	8.43E+09	2.67E+03
304	0.0	1.27E-10	0.21519	2.94E+03	8.54E+09	3.19E+03
305	0.0	1.49E-10	0.21526	2.94E+03	8.65E+09	3.80E+03
306	0.0	1.76E-10	0.21435	2.93E+03	8.77E+09	4.51E+03
307	0.0	2.07E-10	0.21694	2.96E+03	8.88E+09	5.44E+03
308	0.0	2.43E-10	0.21586	2.95E+03	9.00E+09	6.45E+03
309	0.0	2.86E-10	0.21853	2.99E+03	9.12E+09	7.79E+03
310	0.0	3.37E-10	0.22087	3.02E+03	9.24E+09	9.38E+03
311	0.0	3.96E-10	0.22553	3.08E+03	9.35E+09	1.14E+04
312	0.0	4.66E-10	0.22340	3.05E+03	9.48E+09	1.35E+04
313	0.0	5.48E-10	0.22507	3.07E+03	9.60E+09	1.62E+04
314	0.0	6.45E-10	0.22979	3.14E+03	9.72E+09	1.97E+04
315	0.0	7.59E-10	0.23324	3.19E+03	9.85E+09	2.38E+04
316	0.0	8.93E-10	0.23250	3.18E+03	9.97E+09	2.83E+04
317	0.0	1.05E-09	0.23689	3.24E+03	1.01E+10	3.43E+04
318	0.0	1.24E-09	0.23632	3.23E+03	1.02E+10	4.08E+04
319	0.0	1.45E-09	0.23965	3.27E+03	1.04E+10	4.93E+04
320	0.0	1.71E-09	0.24190	3.30E+03	1.05E+10	5.92E+04
321	0.0	2.01E-09	0.24406	3.33E+03	1.06E+10	7.12E+04
322	0.0	2.37E-09	0.24157	3.30E+03	1.08E+10	8.40E+04
323	0.0	2.78E-09	0.24272	3.32E+03	1.09E+10	1.00E+05
324	0.0	3.28E-09	0.23967	3.27E+03	1.10E+10	1.18E+05
325	0.0	3.85E-09	0.24160	3.30E+03	1.12E+10	1.42E+05
326	0.0	4.53E-09	0.24599	3.36E+03	1.13E+10	1.72E+05
327	0.0	5.33E-09	0.25254	3.45E+03	1.14E+10	2.10E+05
328	0.0	6.27E-09	0.24705	3.37E+03	1.16E+10	2.45E+05
329	0.0	7.38E-09	0.24674	3.37E+03	1.17E+10	2.92E+05
330	0.0	8.68E-09	0.24339	3.32E+03	1.19E+10	3.42E+05
331	0.0	1.02E-08	0.24537	3.35E+03	1.20E+10	4.11E+05
332	0.0	1.20E-08	0.24081	3.29E+03	1.21E+10	4.80E+05
333	0.0	1.41E-08	0.23770	3.25E+03	1.23E+10	5.65E+05
334	0.0	1.66E-08	0.23951	3.27E+03	1.24E+10	6.77E+05
335	0.0	1.96E-08	0.23365	3.19E+03	1.26E+10	7.87E+05
336	0.0	2.30E-08	0.23304	3.18E+03	1.27E+10	9.34E+05
337	0.0	2.71E-08	0.23120	3.16E+03	1.29E+10	1.10E+06
338	0.0	3.19E-08	0.22944	3.13E+03	1.31E+10	1.30E+06
339	0.0	3.75E-08	0.22778	3.11E+03	1.32E+10	1.54E+06
340	0.0	4.41E-08	0.22816	3.12E+03	1.34E+10	1.84E+06
341	0.0	5.19E-08	0.22390	3.06E+03	1.35E+10	2.15E+06
342	0.0	6.11E-08	0.22373	3.06E+03	1.37E+10	2.55E+06
343	0.0	7.18E-08	0.21651	2.96E+03	1.38E+10	2.94E+06
344	0.0	8.45E-08	0.21792	2.98E+03	1.40E+10	3.52E+06

345	0.0	9.94E-08	0.21107	2.88E+03	1.42E+10	4.06E+06
346	0.0	1.17E-07	0.20749	2.83E+03	1.43E+10	4.75E+06
347	0.0	1.38E-07	0.20697	2.83E+03	1.45E+10	5.64E+06
348	0.0	1.62E-07	0.19809	2.71E+03	1.47E+10	6.43E+06
349	0.0	1.90E-07	0.19795	2.70E+03	1.48E+10	7.64E+06
350	0.0	2.24E-07	0.19500	2.66E+03	1.50E+10	8.96E+06
351	0.0	2.64E-07	0.19147	2.62E+03	1.52E+10	1.05E+07
352	0.0	3.10E-07	0.18826	2.57E+03	1.54E+10	1.22E+07
353	0.0	3.65E-07	0.18656	2.55E+03	1.55E+10	1.44E+07
354	0.0	4.29E-07	0.18871	2.58E+03	1.57E+10	1.74E+07
355	0.0	5.05E-07	0.18434	2.52E+03	1.59E+10	2.02E+07
356	0.0	5.94E-07	0.18022	2.46E+03	1.61E+10	2.35E+07
357	0.0	6.99E-07	0.17767	2.43E+03	1.62E+10	2.76E+07
358	0.0	8.22E-07	0.17825	2.44E+03	1.64E+10	3.29E+07
359	0.0	9.67E-07	0.17310	2.36E+03	1.66E+10	3.80E+07
360	0.0	1.14E-06	0.17237	2.35E+03	1.68E+10	4.50E+07
361	0.1	1.34E-06	0.16836	2.30E+03	1.70E+10	5.23E+07
362	0.1	1.58E-06	0.16702	2.28E+03	1.72E+10	6.17E+07
363	0.1	1.85E-06	0.16859	2.30E+03	1.74E+10	7.41E+07
364	0.1	2.18E-06	0.16344	2.23E+03	1.76E+10	8.55E+07
365	0.1	2.57E-06	0.16414	2.24E+03	1.77E+10	1.02E+08
366	0.1	3.02E-06	0.15597	2.13E+03	1.79E+10	1.15E+08
367	0.1	3.55E-06	0.15387	2.10E+03	1.81E+10	1.35E+08
368	0.2	4.18E-06	0.15261	2.08E+03	1.83E+10	1.60E+08
369	0.2	4.91E-06	0.15003	2.05E+03	1.85E+10	1.87E+08
370	0.2	5.78E-06	0.14939	2.04E+03	1.87E+10	2.21E+08
371	0.3	6.80E-06	0.14719	2.01E+03	1.89E+10	2.59E+08
372	0.3	8.00E-06	0.14995	2.05E+03	1.92E+10	3.14E+08
373	0.4	9.41E-06	0.13708	1.87E+03	1.94E+10	3.41E+08
374	0.4	1.11E-05	0.12607	1.72E+03	1.96E+10	3.73E+08
375	0.5	1.30E-05	0.14257	1.95E+03	1.98E+10	5.02E+08
376	0.6	1.53E-05	0.13941	1.90E+03	2.00E+10	5.83E+08
377	0.7	1.80E-05	0.14002	1.91E+03	2.02E+10	6.97E+08
378	0.8	2.12E-05	0.14484	1.98E+03	2.04E+10	8.57E+08
379	1.0	2.50E-05	0.14040	1.92E+03	2.06E+10	9.88E+08
380	1.1	2.94E-05	0.14928	2.04E+03	2.09E+10	1.25E+09
381	1.3	3.45E-05	0.13826	1.89E+03	2.11E+10	1.37E+09
382	1.6	4.06E-05	0.14022	1.92E+03	2.13E+10	1.66E+09
383	1.9	4.78E-05	0.14364	1.96E+03	2.15E+10	2.02E+09
384	2.2	5.63E-05	0.15200	2.08E+03	2.17E+10	2.54E+09
385	2.6	6.62E-05	0.15034	2.05E+03	2.20E+10	2.99E+09
386	3.0	7.79E-05	0.15330	2.09E+03	2.22E+10	3.62E+09
387	3.6	9.16E-05	0.15207	2.08E+03	2.24E+10	4.27E+09
388	4.2	1.08E-04	0.15893	2.17E+03	2.27E+10	5.30E+09
389	4.9	1.27E-04	0.16699	2.28E+03	2.29E+10	6.62E+09
390	5.8	1.49E-04	0.16795	2.29E+03	2.31E+10	7.92E+09
391	6.8	1.75E-04	0.16759	2.29E+03	2.34E+10	9.39E+09
392	8.0	2.06E-04	0.17638	2.41E+03	2.36E+10	1.17E+10
393	9.4	2.43E-04	0.17909	2.45E+03	2.39E+10	1.42E+10
394	11.1	2.86E-04	0.18052	2.47E+03	2.41E+10	1.70E+10
395	13.1	3.36E-04	0.18739	2.56E+03	2.43E+10	2.09E+10
396	15.3	3.93E-04	0.19133	2.61E+03	2.46E+10	2.53E+10
397	18.4	4.74E-04	0.19851	2.71E+03	2.48E+10	3.19E+10
398	23.1	5.96E-04	0.20468	2.80E+03	2.51E+10	4.18E+10

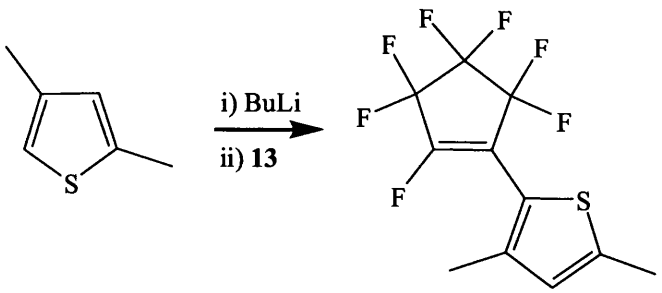
399	29.3	7.55E-04	0.21310	2.91E+03	2.53E+10	5.57E+10
400	36.9	9.49E-04	0.21510	2.94E+03	2.56E+10	7.14E+10
401	46.2	1.19E-03	0.22132	3.02E+03	2.59E+10	9.30E+10
402	58.1	1.50E-03	0.22852	3.12E+03	2.61E+10	1.22E+11
403	72.7	1.87E-03	0.23416	3.20E+03	2.64E+10	1.58E+11
404	89.2	2.30E-03	0.24063	3.29E+03	2.66E+10	2.01E+11
405	108.1	2.78E-03	0.24101	3.29E+03	2.69E+10	2.46E+11
406	130.7	3.37E-03	0.25037	3.42E+03	2.72E+10	3.13E+11
407	156.1	4.02E-03	0.25408	3.47E+03	2.74E+10	3.83E+11
408	183.2	4.72E-03	0.26242	3.58E+03	2.77E+10	4.69E+11
409	212.7	5.48E-03	0.27238	3.72E+03	2.80E+10	5.70E+11
410	244.1	6.29E-03	0.27150	3.71E+03	2.83E+10	6.59E+11
411	279.1	7.19E-03	0.27912	3.81E+03	2.85E+10	7.82E+11
412	317.4	8.17E-03	0.28181	3.85E+03	2.88E+10	9.07E+11
413	355.7	9.16E-03	0.28963	3.96E+03	2.91E+10	1.05E+12
414	395.0	1.02E-02	0.29608	4.04E+03	2.94E+10	1.21E+12
415	436.0	1.12E-02	0.30511	4.17E+03	2.97E+10	1.39E+12
416	476.8	1.23E-02	0.30442	4.16E+03	2.99E+10	1.53E+12
417	516.5	1.33E-02	0.31032	4.24E+03	3.02E+10	1.70E+12
418	556.8	1.43E-02	0.31837	4.35E+03	3.05E+10	1.90E+12
419	598.8	1.54E-02	0.31799	4.34E+03	3.08E+10	2.06E+12
420	635.6	1.64E-02	0.32518	4.44E+03	3.11E+10	2.26E+12
421	661.7	1.70E-02	0.32758	4.48E+03	3.14E+10	2.40E+12
422	680.1	1.75E-02	0.33146	4.53E+03	3.17E+10	2.51E+12
423	694.4	1.79E-02	0.33887	4.63E+03	3.20E+10	2.65E+12
424	706.5	1.82E-02	0.34014	4.65E+03	3.23E+10	2.73E+12
425	716.6	1.85E-02	0.34565	4.72E+03	3.26E+10	2.84E+12
426	721.6	1.86E-02	0.34845	4.76E+03	3.29E+10	2.91E+12
427	720.5	1.86E-02	0.35375	4.83E+03	3.32E+10	2.98E+12
428	714.9	1.84E-02	0.35221	4.81E+03	3.36E+10	2.97E+12
429	705.9	1.82E-02	0.35506	4.85E+03	3.39E+10	2.99E+12
430	697.9	1.80E-02	0.35715	4.88E+03	3.42E+10	3.00E+12
431	691.2	1.78E-02	0.35853	4.90E+03	3.45E+10	3.01E+12
432	683.6	1.76E-02	0.36167	4.94E+03	3.48E+10	3.03E+12
433	673.6	1.73E-02	0.36106	4.93E+03	3.52E+10	3.01E+12
434	663.1	1.71E-02	0.36060	4.93E+03	3.55E+10	2.98E+12
435	655.6	1.69E-02	0.36118	4.93E+03	3.58E+10	2.98E+12
436	649.0	1.67E-02	0.36131	4.94E+03	3.61E+10	2.98E+12
437	641.6	1.65E-02	0.36245	4.95E+03	3.65E+10	2.98E+12
438	636.3	1.64E-02	0.36052	4.93E+03	3.68E+10	2.97E+12
439	633.0	1.63E-02	0.35720	4.88E+03	3.71E+10	2.95E+12
440	629.3	1.62E-02	0.35940	4.91E+03	3.75E+10	2.98E+12
441	626.7	1.61E-02	0.35625	4.87E+03	3.78E+10	2.97E+12
442	625.5	1.61E-02	0.35293	4.82E+03	3.82E+10	2.96E+12
443	622.7	1.60E-02	0.35349	4.83E+03	3.85E+10	2.98E+12
444	617.6	1.59E-02	0.34824	4.76E+03	3.89E+10	2.94E+12
445	610.6	1.57E-02	0.34620	4.73E+03	3.92E+10	2.92E+12
446	603.0	1.55E-02	0.34356	4.69E+03	3.96E+10	2.88E+12
447	595.8	1.53E-02	0.34058	4.65E+03	3.99E+10	2.85E+12
448	588.2	1.51E-02	0.33966	4.64E+03	4.03E+10	2.83E+12
449	578.1	1.49E-02	0.33458	4.57E+03	4.06E+10	2.77E+12
450	566.0	1.46E-02	0.32820	4.48E+03	4.10E+10	2.68E+12
451	552.7	1.42E-02	0.32380	4.42E+03	4.14E+10	2.60E+12
452	536.7	1.38E-02	0.31776	4.34E+03	4.17E+10	2.50E+12

453	519.1	1.34E-02	0.31473	4.30E+03	4.21E+10	2.42E+12
454	500.9	1.29E-02	0.31040	4.24E+03	4.25E+10	2.32E+12
455	482.0	1.24E-02	0.30402	4.15E+03	4.29E+10	2.21E+12
456	463.3	1.19E-02	0.29748	4.06E+03	4.32E+10	2.10E+12
457	445.5	1.15E-02	0.28970	3.96E+03	4.36E+10	1.98E+12
458	429.9	1.11E-02	0.28247	3.86E+03	4.40E+10	1.88E+12
459	417.2	1.07E-02	0.27740	3.79E+03	4.44E+10	1.81E+12
460	403.3	1.04E-02	0.27040	3.69E+03	4.48E+10	1.72E+12
461	386.2	9.94E-03	0.26422	3.61E+03	4.52E+10	1.62E+12
462	367.7	9.47E-03	0.25602	3.50E+03	4.56E+10	1.51E+12
463	350.3	9.02E-03	0.24926	3.41E+03	4.60E+10	1.41E+12
464	336.2	8.66E-03	0.24253	3.31E+03	4.64E+10	1.33E+12
465	325.5	8.38E-03	0.23492	3.21E+03	4.68E+10	1.26E+12
466	313.9	8.08E-03	0.22631	3.09E+03	4.72E+10	1.18E+12
467	300.2	7.73E-03	0.21952	3.00E+03	4.76E+10	1.10E+12
468	287.5	7.40E-03	0.21111	2.88E+03	4.80E+10	1.02E+12
469	276.4	7.12E-03	0.20143	2.75E+03	4.84E+10	9.48E+11
470	266.5	6.86E-03	0.19440	2.66E+03	4.88E+10	8.89E+11
471	257.9	6.64E-03	0.18548	2.53E+03	4.92E+10	8.28E+11
472	250.2	6.44E-03	0.18043	2.46E+03	4.96E+10	7.88E+11
473	242.2	6.24E-03	0.17004	2.32E+03	5.01E+10	7.25E+11
474	233.8	6.02E-03	0.16201	2.21E+03	5.05E+10	6.73E+11
475	225.3	5.80E-03	0.15575	2.13E+03	5.09E+10	6.28E+11
476	217.4	5.60E-03	0.14806	2.02E+03	5.13E+10	5.81E+11
477	210.1	5.41E-03	0.14030	1.92E+03	5.18E+10	5.37E+11
478	203.6	5.24E-03	0.13242	1.81E+03	5.22E+10	4.95E+11
479	196.9	5.07E-03	0.12574	1.72E+03	5.26E+10	4.58E+11
480	189.4	4.88E-03	0.11953	1.63E+03	5.31E+10	4.23E+11
481	181.9	4.68E-03	0.11143	1.52E+03	5.35E+10	3.82E+11
482	174.6	4.50E-03	0.10605	1.45E+03	5.40E+10	3.52E+11
483	166.7	4.29E-03	0.09774	1.34E+03	5.44E+10	3.12E+11
484	159.4	4.10E-03	0.09427	1.29E+03	5.49E+10	2.90E+11
485	153.2	3.94E-03	0.08812	1.20E+03	5.53E+10	2.63E+11
486	146.7	3.78E-03	0.08110	1.11E+03	5.58E+10	2.33E+11
487	139.2	3.58E-03	0.07649	1.05E+03	5.62E+10	2.11E+11
488	131.2	3.38E-03	0.07267	9.93E+02	5.67E+10	1.90E+11
489	123.8	3.19E-03	0.06739	9.21E+02	5.72E+10	1.68E+11
490	117.8	3.03E-03	0.06340	8.66E+02	5.76E+10	1.51E+11
491	112.4	2.89E-03	0.05812	7.94E+02	5.81E+10	1.34E+11
492	107.0	2.76E-03	0.05420	7.40E+02	5.86E+10	1.20E+11
493	101.9	2.62E-03	0.04865	6.65E+02	5.91E+10	1.03E+11
494	96.8	2.49E-03	0.04629	6.32E+02	5.96E+10	9.38E+10
495	91.3	2.35E-03	0.04252	5.81E+02	6.00E+10	8.20E+10
496	86.5	2.23E-03	0.04069	5.56E+02	6.05E+10	7.49E+10
497	82.2	2.12E-03	0.03632	4.96E+02	6.10E+10	6.41E+10
498	78.2	2.01E-03	0.03419	4.67E+02	6.15E+10	5.78E+10
499	74.5	1.92E-03	0.03195	4.36E+02	6.20E+10	5.19E+10
500	71.1	1.83E-03	0.02889	3.95E+02	6.25E+10	4.51E+10
501	67.7	1.74E-03	0.02648	3.62E+02	6.30E+10	3.97E+10
502	64.5	1.66E-03	0.02368	3.24E+02	6.35E+10	3.41E+10
503	61.2	1.57E-03	0.02126	2.90E+02	6.40E+10	2.93E+10
504	57.8	1.49E-03	0.02055	2.81E+02	6.45E+10	2.70E+10
505	55.1	1.42E-03	0.01820	2.49E+02	6.50E+10	2.30E+10
506	53.2	1.37E-03	0.01640	2.24E+02	6.56E+10	2.01E+10

507	51.6	1.33E-03	0.01496	2.04E+02	6.61E+10	1.80E+10
508	49.7	1.28E-03	0.01267	1.73E+02	6.66E+10	1.48E+10
509	47.2	1.22E-03	0.01377	1.88E+02	6.71E+10	1.53E+10
510	44.9	1.16E-03	0.01177	1.61E+02	6.77E+10	1.26E+10
511	43.6	1.12E-03	0.01071	1.46E+02	6.82E+10	1.12E+10
512	42.1	1.08E-03	0.00974	1.33E+02	6.87E+10	9.92E+09
513	39.7	1.02E-03	0.00862	1.18E+02	6.93E+10	8.33E+09
514	37.1	9.56E-04	0.00840	1.15E+02	6.98E+10	7.66E+09
515	34.9	9.00E-04	0.00726	9.92E+01	7.03E+10	6.28E+09
516	33.0	8.50E-04	0.00583	7.96E+01	7.09E+10	4.80E+09
517	31.3	8.05E-04	0.00658	8.99E+01	7.14E+10	5.17E+09
518	29.8	7.67E-04	0.00609	8.31E+01	7.20E+10	4.59E+09
519	28.2	7.26E-04	0.00445	6.09E+01	7.26E+10	3.21E+09
520	26.4	6.79E-04	0.00453	6.19E+01	7.31E+10	3.07E+09
521	24.8	6.38E-04	0.00504	6.88E+01	7.37E+10	3.23E+09
522	23.4	6.03E-04	0.00418	5.72E+01	7.42E+10	2.56E+09
523	22.2	5.71E-04	0.00402	5.49E+01	7.48E+10	2.34E+09
524	21.1	5.43E-04	0.00314	4.29E+01	7.54E+10	1.76E+09
525	20.0	5.16E-04	0.00304	4.15E+01	7.60E+10	1.63E+09
526	18.9	4.86E-04	0.00323	4.42E+01	7.65E+10	1.64E+09
527	17.8	4.57E-04	0.00271	3.71E+01	7.71E+10	1.31E+09
528	16.9	4.35E-04	0.00216	2.95E+01	7.77E+10	9.98E+08
529	16.2	4.17E-04	0.00178	2.44E+01	7.83E+10	7.97E+08
530	15.4	3.96E-04	0.00165	2.25E+01	7.89E+10	7.02E+08
531	14.4	3.71E-04	0.00127	1.73E+01	7.95E+10	5.12E+08
532	13.7	3.52E-04	0.00122	1.66E+01	8.01E+10	4.68E+08
533	13.0	3.34E-04	0.00141	1.92E+01	8.07E+10	5.19E+08
534	12.3	3.17E-04	0.00155	2.11E+01	8.13E+10	5.44E+08
535	11.4	2.93E-04	0.00137	1.87E+01	8.19E+10	4.49E+08
536	10.3	2.66E-04	0.00000	7.80E-03	8.25E+10	1.71E+05
537	9.6	2.47E-04	0.00051	6.99E+00	8.32E+10	1.44E+08
538	9.2	2.37E-04	0.00173	2.36E+01	8.38E+10	4.70E+08
539	9.0	2.31E-04	0.00082	1.12E+01	8.44E+10	2.17E+08
540	8.6	2.23E-04	0.00128	1.75E+01	8.50E+10	3.32E+08
541	8.3	2.14E-04	0.00121	1.65E+01	8.57E+10	3.03E+08
542	8.0	2.06E-04	0.00073	9.94E+00	8.63E+10	1.77E+08
543	7.7	1.97E-04	0.00093	1.27E+01	8.69E+10	2.18E+08
544	7.3	1.87E-04	0.00098	1.34E+01	8.76E+10	2.20E+08
545	6.9	1.78E-04	0.00129	1.76E+01	8.82E+10	2.76E+08
546	6.6	1.70E-04	0.00020	2.73E+00	8.89E+10	4.13E+07
547	6.3	1.62E-04	0.00090	1.24E+01	8.95E+10	1.80E+08
548	6.1	1.56E-04	0.00000	0.00E+00	9.02E+10	0.00E+00
549	5.9	1.52E-04	0.00062	8.41E+00	9.08E+10	1.16E+08
550	5.8	1.48E-04	0.00057	7.83E+00	9.15E+10	1.06E+08
551	5.8	1.48E-04	0.00124	1.70E+01	9.22E+10	2.32E+08
552	5.8	1.48E-04	0.00000	0.00E+00	9.28E+10	0.00E+00
553	5.8	1.48E-04	0.00062	8.41E+00	9.35E+10	1.17E+08
554	5.8	1.48E-04	0.00115	1.57E+01	9.42E+10	2.19E+08
555	5.8	1.48E-04	0.00035	4.83E+00	9.49E+10	6.79E+07
556	5.8	1.48E-04	0.00093	1.27E+01	9.56E+10	1.80E+08
557	5.8	1.48E-04	0.00000	0.00E+00	9.63E+10	0.00E+00
558	5.8	1.48E-04	0.00073	1.00E+01	9.69E+10	1.44E+08
559	5.8	1.48E-04	0.00044	5.99E+00	9.76E+10	8.67E+07
560	5.8	1.48E-04	0.00140	1.91E+01	9.83E+10	2.79E+08

561	5.8	1.48E-04	0.00043	5.83E+00	9.90E+10		8.56E+07
562	5.8	1.48E-04	0.00000	0.00E+00	9.98E+10		0.00E+00
563	5.8	1.48E-04	0.00014	1.85E+00	1.00E+11		2.75E+07
564	5.8	1.48E-04	0.00090	1.24E+01	1.01E+11		1.85E+08
565	5.8	1.48E-04	0.00045	6.13E+00	1.02E+11		9.26E+07
566	5.8	1.48E-04	0.00014	1.85E+00	1.03E+11		2.81E+07
567	5.8	1.48E-04	0.00000	0.00E+00	1.03E+11		0.00E+00
568	5.8	1.48E-04	0.00000	0.00E+00	1.04E+11		0.00E+00
569	5.8	1.48E-04	0.00021	2.85E+00	1.05E+11		4.44E+07
570	5.8	1.48E-04	0.00018	2.49E+00	1.06E+11		3.90E+07
571	5.8	1.48E-04	0.00000	0.00E+00	1.06E+11		0.00E+00
572	5.8	1.48E-04	0.00177	2.42E+01	1.07E+11		3.85E+08
573	5.8	1.48E-04	0.00011	1.50E+00	1.08E+11		2.40E+07
574	5.8	1.48E-04	0.00001	1.46E-01	1.09E+11		2.35E+06
575	5.8	1.48E-04	0.00000	0.00E+00	1.09E+11		0.00E+00
576	5.8	1.48E-04	0.00100	1.36E+01	1.10E+11		2.22E+08
577	5.8	1.48E-04	0.00079	1.08E+01	1.11E+11		1.77E+08
578	5.8	1.48E-04	0.00000	0.00E+00	1.12E+11		0.00E+00
579	5.8	1.48E-04	0.00069	9.47E+00	1.12E+11		1.58E+08
580	5.8	1.48E-04	0.00083	1.13E+01	1.13E+11		1.89E+08
581	5.8	1.48E-04	0.00117	1.60E+01	1.14E+11		2.70E+08
582	5.8	1.48E-04	0.00025	3.38E+00	1.15E+11		5.75E+07
583	5.8	1.48E-04	0.00043	5.84E+00	1.16E+11		1.00E+08
584	5.8	1.48E-04	0.00117	1.60E+01	1.16E+11		2.76E+08
585	5.8	1.48E-04	0.00065	8.94E+00	1.17E+11		1.55E+08
586	5.8	1.48E-04	0.00125	1.70E+01	1.18E+11		2.98E+08
587	5.8	1.48E-04	0.00012	1.58E+00	1.19E+11		2.79E+07
588	5.8	1.48E-04	0.00016	2.13E+00	1.20E+11		3.77E+07
589	5.8	1.48E-04	0.00091	1.24E+01	1.20E+11		2.21E+08
590	5.8	1.48E-04	0.00073	9.95E+00	1.21E+11		1.79E+08
591	5.8	1.48E-04	0.00069	9.43E+00	1.22E+11		1.71E+08
592	5.8	1.48E-04	0.00072	9.88E+00	1.23E+11		1.80E+08
593	5.8	1.48E-04	0.00044	5.98E+00	1.24E+11		1.10E+08
594	5.8	1.48E-04	0.00059	8.10E+00	1.24E+11		1.50E+08
595	5.8	1.48E-04	0.00077	1.06E+01	1.25E+11		1.96E+08
596	5.8	1.48E-04	0.00041	5.58E+00	1.26E+11		1.04E+08
597	5.8	1.48E-04	0.00035	4.76E+00	1.27E+11		8.97E+07
598	5.8	1.48E-04	0.00092	1.26E+01	1.28E+11		2.39E+08
599	5.8	1.48E-04	0.00038	5.23E+00	1.29E+11		9.98E+07
600	5.8	1.48E-04	0.00081	1.11E+01	1.30E+11		2.13E+08
	SUM	SUM					
	39,837.6903	1.0			Spectral Overlap Integral $dm^3mol^{-1}cm^{-1}nm^4$	J	1.49E+14
					Forster Distance Angstroms	Ro	36.9

3.11.5 Synthesis of 1-(3,5-dimethyl-2-thienyl)perfluorocyclopentene (46).



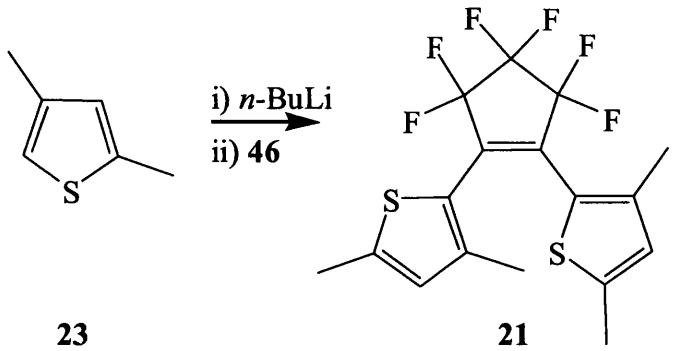
23 **46**

Scheme 3.23: The reaction of 13 with one mole equivalent of 23 *via* lithiation with BuLi to form 46 as reported by Uchida and Irie.[50]

2,4-Dimethylthiophene (**23**, 4.20 g, 37 mmol) was dissolved in dry distilled tetrahydrofuran (100 mL) in a 250 mL round-bottomed flask that had been dried in an oven overnight and flushed with argon. This colourless solution was cooled in ice/water. Butyllithium (15 mL of a 2.5 mol dm^{-3} solution in pentane, 37.5 mmol) was added dropwise to the reaction vessel. The resulting bright yellow solution was stirred for 90 min. The resulting solution of lithiated 2,4-dimethylthiophene was cooled to -30 °C and added dropwise by syringe to a solution of octafluorocyclopentene (**13**, 7.94 g, 37.4 mmol collected in an ice-cooled trap and dissolved in 150 mL THF) which had also been cooled to -30 °C. The reaction mixture turned dark blue. The solution was stirred for 1 hour and allowed to warm to room temperature. Aqueous hydrochloric acid (2M, 100 mL) was added to the mixture. The mixture was extracted with diethyl ether (3 x 120 mL). The organic phase was washed with saturated aqueous sodium chloride solution and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was purified by distillation under reduced pressure. The product **46** was isolated as a clear colourless oil in 87% yield (9.91 g, 32.5 mmol) and 96.5 % purity (GC). ν_{max} (film) /cm^{-1} 2889. δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.14 (3H, s, 3-C*H*$_3$), 2.39 (3H, s, 5-C*H*$_3$), 6.58 (1H, s, C*H*). δ_C (100 MHz, $CDCl_3$; Me_4Si) 15.5, 15.8 (2 x *C*H$_3$), 110.5 (tm, $^1J_{C\text{-}F}$ = 272 Hz perfluorocyclopentenyl 4-*C*), 111.3 (tm, $^1J_{C\text{-}F}$ = 267 Hz, perfluorocyclopentenyl 5-*C*), 115.3 (tm, $^1J_{C\text{-}F}$ = 267 Hz perfluorocyclopentenyl 3-*C* + thienyl 2-*C* overlaid at the centre of the tm), 118.7 (m, perfluorocyclopentenyl 2-*C*), 130.2 (thienyl 4-*C*H), 143.2 (thienyl 3-*C*), 145.3 (thienyl 5-*C*), 149.8 (dm, $^1J_{C\text{-}F}$ = 296 Hz perfluorocyclopentenyl 1-*C*) . δ_F (376 MHz, $CDCl_3$) -129.6 (4-*F*), -117.4 (1-*F*), -108.2

(3-*F* + 5-*F*). *m/z* (EI^+) = 304.0149 ($[M]^+$ $C_{11}H_7F_7S$ requires 304.01451). *m/z* (EI^+) = 304 (20 %), 289 ($[M-CH_3]^+$ 16 %), 285 ($[M-F]^+$ 4%), 100 (16 %), 69 (100 %), 39 (42 %).

3.11.6 *Synthesis of 21 from 23 and 46.*

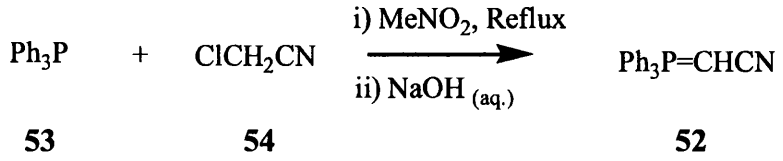


23 **21**

Scheme 3.24: Reaction of 26 with 46 via lithiation with BuLi to form 21, as reported by Uchida and Irie.[50]

2,4-Dimethylthiophene (**23**, 0.282 g, 2.39 mmol) was dissolved in dry distilled tetrahydrofuran (10 mL) in a 25 mL round-bottomed flask that had been dried in an oven overnight and flushed with argon. This colourless solution was cooled in ice/water. Butyllithium (1.6 mL of a 2.5 mol dm^{-3} pentane solution) was added dropwise to the reaction vessel and the solution turned yellow. The solution was stirred for 90 minutes. 1-(3,5-Dimethyl-2-thienyl)-perfluorocyclopentene (**46**, 0.727 g, 2.39 mmol) was added dropwise by syringe. The reaction mixture turned dark blue. The solution was stirred for 1 hour and allowed to warm to room temperature. Saturated aqueous ammonium chloride (10 mL) was added to the mixture. Diethyl ether (20 mL) was added to the mixture, the organic phase was separated and the aqueous phase washed with diethyl ether (2 x 10 mL). The organic phase was washed with saturated aqueous sodium chloride and dried with anhydrous magnesium sulfate. The mixture was qualitatively analysed by TLC and GC. The solvent was removed under reduced pressure and the product was purified by column chromatography (hexane) and recrystallised from hexane. The expected product **21** was isolated as yellow prisms, (mp 129.3-131.0 °C, lit.[50] 130 °C) in 83% yield (0.826 g, 2.09 mmol) and 96% purity (GC). The sample was identical in all respects to the product of the 1-step reaction.

3.11.7 *Synthesis of (triphenyl-λ^5-phosphanylidene)acetonitrile (52).*

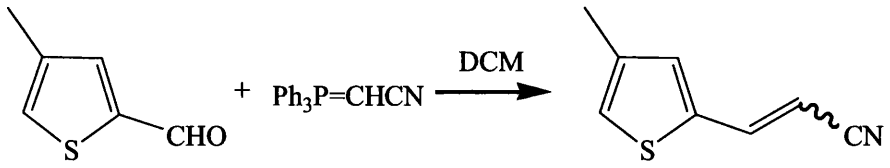


Scheme 3.25: The synthesis of 52 by i) reaction of triphenylphosphine (53) and chloroacetonitrile (54) to form the hydrochloride salt and ii) reaction with NaOH to form 52.

Triphenylphosphine (**53**, 10.3 g, 39.3 mmol) and cyanoacetonitrile (**54**, 3.07 g, 40.7 mmol) were dissolved in distilled nitromethane (100 mL) in a 250 mL round-bottomed flask. The flask was fitted with a condenser and the reaction was refluxed at 115 °C overnight. As the solution cooled the product precipitated out. The product, cyanomethylphosphonium chloride was removed from the solution by Büchner filtration and washed with diethyl ether. The product was isolated in 61 % yield (8.09 g, 24.0 mmol).

The product of the previous reaction, cyanomethylphosphonium chloride (7.45 g, 22.0 mmol) was dissolved in distilled water (50 mL). The aqueous solution was washed with dichloromethane (2 x 40 mL) to remove any organic material, and then aqueous sodium hydroxide solution (1.68 g, 42 mmol in 30 mL H_2O) was added. The product, (triphenyl-λ^5-phosphanylidene)acetonitrile, was observed immediately to precipitate out as a white solid. The mixture was stirred for 10 minutes. The reaction mixture was washed with dichloromethane (2 x mL), at which point the white precipitate disappeared. The organic phase was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was recrystallised from diethyl ether. The product **52** was isolated as white crystals mp 192.3-193.6 °C (lit.[95]195.5 °C) in 52 % overall yield (5.63 g). ν_{max} (film) /cm^{-1} 2137 (CN). δ_H (400 MHz, $CDCl_3$, Me_3Si) 2.09 (1H, m, C*H*), 7.54 (6H, m, phenyl *meta*-C*H*), 7.62 (3H, m, phenyl *para*-C*H*), 7.74 (6H, m, phenyl *ortho*-C*H*).

3.11.8 *Synthesis of **50** via the Wittig reaction of **51** and **52**.*

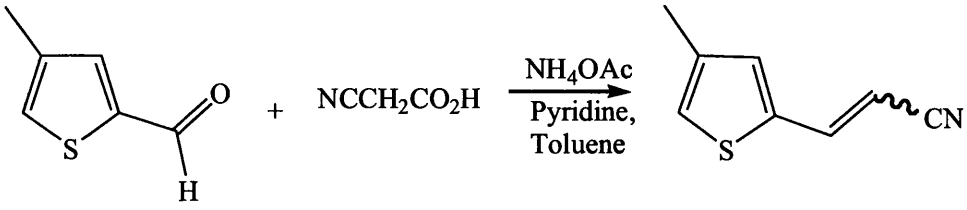


51 **52** **50**

Scheme 3.26: Wittig reaction of 51 with (triphenyl-λ^5-phosphanylidene)acetonitrile (52) in dichloromethane (DCM) to form 50.

(Triphenyl-λ^5-phosphanylidene)acetonitrile (**52**, 0.520 g, 1.73 mmol) and 4-methyl-2-thiophenecarboxaldehyde (**51**, 0.144 g, 1.14 mmol) were dissolved in dichloromethane (15 mL) in a 25 mL round-bottomed flask. The flask was fitted with a condenser and the mixture was refluxed overnight. The mixture was monitored by TLC. Saturated aqueous ammonium chloride was added to the mixture, and the organic phase was further washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was purified by silica gel chromatography (50% Et_2O/hexane). The product **50** was isolated as an light green oil (bp 287 °C) in 88 % yield (0.15 g, 1.01 mmol) and 98% purity (GC). *E*:*Z* ratio = 5:1 (GC/NMR). ν_{max} (film) /cm^{-1} 2137 (CN). δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.29 (3H, s, C*H*$_3$), 5.22 (0.2H, d, *J* = 12 Hz, *Z*-isomer CH=C*H*CN), 5.60 (0.8H, d, *J* = 16 Hz, *E*-isomer CH=C*H*CN), 6.95 (1H, s, thienyl 3-C*H*), 7.05 (1H, s, thienyl 5-*H*), 7.12 (0.2H, d, *J* = 12 Hz, *Z*-isomer C*H*=CHCN), 7.39 (0.8H, d, *J* = 16 Hz, *E*-isomer C*H*=CHCN). δ_C (100 MHz; $CDCl_3$ Me_4Si).15.88 (*C*H$_3$), 91.6 (*Z*-isomer CH=*C*HCN), 94.2 (*E*-isomer CH=*C*HCN), 118.1 (*Z*-isomer *C*N), 118.6 (*E*-isomer *C*N), 125.6 (*E*-isomer thienyl 5-*C*H), 127.3 (*Z*-isomer thienyl 5-*C*H), 133.7 (*E*-isomer thienyl 3-*C*H), 134.5 (*Z*-isomer thienyl 3-*C*H), 137.8 (*Z*-isomer thienyl 2-*C*), 138.5 (*E*-isomer thienyl 2-*C*), 138.9 (*Z*-isomer thienyl 4-*C*), 141.3 (*Z*-isomer *C*H=CHCN), 143.3 (*E*-isomer *C*H=CHCN). *m/z* (ES^+) = 167.0637 ($[M+NH_4]^+$ $C_8H_{11}N_2S$ requires 167.0637). *m/z* (EI^+) = 149 ($[M]^+$ 20 %), 122 ($[M-CN]^+$ 5 %), 69 (20 %), 45 (100 %). *m/z* (CI^+ (NH_3)) = 167 ($[M+NH_4]^+$ 100 %), 149 ($[M]^+$ 8 %).

3.11.9 *Synthesis of **50** via the reaction of **51** and **57**.*

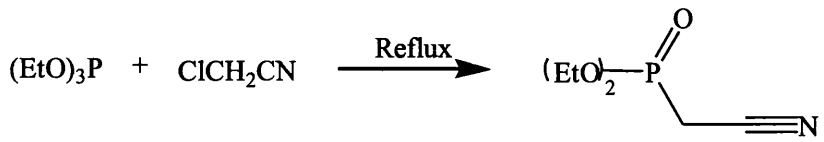


51 **57** **50**

Scheme 3.27: Knoevenagel-type reaction of 51 with cyanoacetic acid (57) to form 50.

4-Methyl-2-thiophenecarboxaldehyde (**51**, 0.165 g, 1.31 mmol), cyanoacetic acid (**57**, 0.115 g, 1.36 mmol), ammonium acetate (0.04 g), pyridine (1 mL) and toluene (3 mL) were placed in a 10 mL round-bottomed flask equipped with a condenser and Dean & Stark trap filled with toluene. The mixture was refluxed at 120 °C for three nights while monitored by TLC. After cooling to room temperature, dichloromethane (20 mL) was added. This solution was washed with saturated sodium chloride (20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was purified by silica gel chromatography (50% Et_2O/hexane) and reduced-pressure distillation. The product **50** was isolated as an light green oil in 84 % yield (0.164 g 1.09 mmol) and 96% purity (GC). *E*:*Z* isomer ratio = 2.5:1 (GC/NMR). Sample is identical in all other respects to the product of the Wittig reaction.

3.11.10 *Synthesis of diethylcyanomethylphosphonate (**55**).*



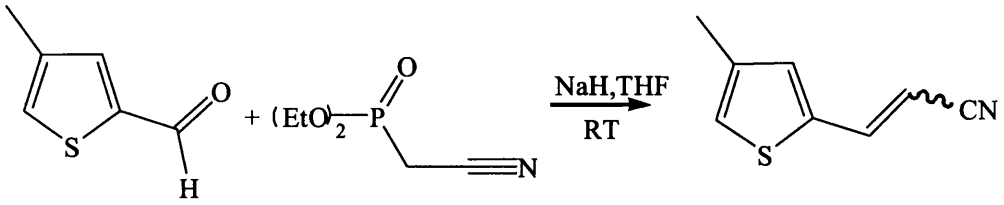
56 **54** **55**

Scheme 3.28: The neat Arbusov reaction of diethyl phosphite (56) with 54 to form 55.

Triethyl phosphite (**56**, 11.41 g, 68.7 mmol) was placed into a 50 mL round-bottomed flask fitted with an air condenser and heated to 100 °C. Chloroacetonitrile (**54**, 7.78 g, 103.0 mmol) was added dropwise over a period of 15 minutes. The mixture was heated to 135 °C for four hours and ethyl chloride was given off as a gas. GC monitoring of the reaction showed a reduction in the amount of starting materials and the appearance of a

new product peak. After approximately four hours, once GC monitoring showed that the triethyl phosphite had been consumed, the reaction vessel was fitted with a distillation apparatus and the product was distilled under reduced pressure as a colourless liquid. The product **55** was isolated in 81% yield (9.81 g) and 94 % purity (GC). ν_{max} (film) /cm^{-1} 2190 (CN), 1260 (PO). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.32 (6H, t, J = 8 Hz, CH_3), 2.85 (2H, d, J = 21 Hz, CH_2CN), 4.18 (4H, quintet, J = 8 Hz, CH_3CH_2). δ_C (100 MHz, $CDCl_3$ Me_4Si) 16.1, 17.5 (CH_2CN), 16.7 (CH_3), 64.3 (CH_3CH_2), 113.2 (CN). δ_P (161 MHz, $CDCl_3$) 14.95. *m/z* (ES$^+$) = 178.0627 ([M+H]$^+$ $C_6H_{13}NO_3P$ requires 178.0628). *m/z* (EI$^+$) 178 ([M+H]$^+$, 6 %), 150 ([M-CN]$^+$ 24 %), 137 (26 %), 122 (62 %), 109 (71 %), 81 (88 %), 41 (100%). *m/z* (CI$^+$(NH_3)) = 195 ([M+NH_4]$^+$ 100 %), 178 ([M+H]$^+$ 4 %), 52 (24 %).

*3.11.11 Synthesis of **50** via the reaction of **51** and **55**.*



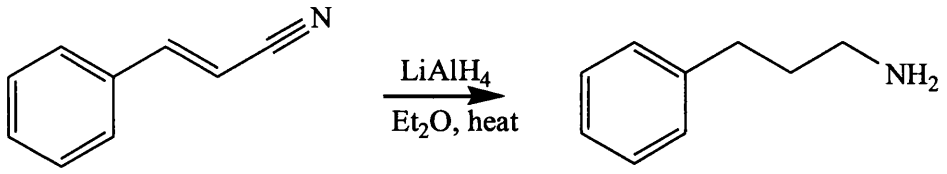
51 **55** **50**

Scheme 3.29: Horner/Wadsworth/Emmons reaction of 51 with diethylcyanomethylphosphonate (55) to form 50.

Sodium hydride (0.10 g of a 60 % dispersion in mineral oil, 2.50 mmol) was washed 3 times successively with dry, distilled hexane (3 x 30 mL) and then suspended in dry, distilled THF (20 mL). To the resulting grey suspension was added diethylcyanomethylphosphonate (**55**, 0.374 g, 2.11 mmol) *via* syringe. The resulting light yellow solution was stirred for 1 hour. 4-Methyl-2-thiophenecarboxaldehyde (**51**, 0.248 g, 1.97 mmol) was added slowly to the solution *via* syringe over 10 min. The resulting thick dark red mixture was stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride solution (10 mL) and extracted with diethyl ether (5 x 25 mL). The organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (25 mL) and saturated aqueous sodium chloride solution (25 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was purified by silica gel chromatography (50% Et_2O/ Hexane) and reduced pressure distillation. The product **50** was isolated as a clear colourless liquid in 91 % yield

(0.267 g, 1.79 mmol) and 98 % purity (GC). *E*:*Z* ratio = 5.5:1 (NMR & GC). Sample was identical in all other respects to the product of the Wittig reaction.

*3.11.12 Reduction of **85** with lithium aluminium hydride.*



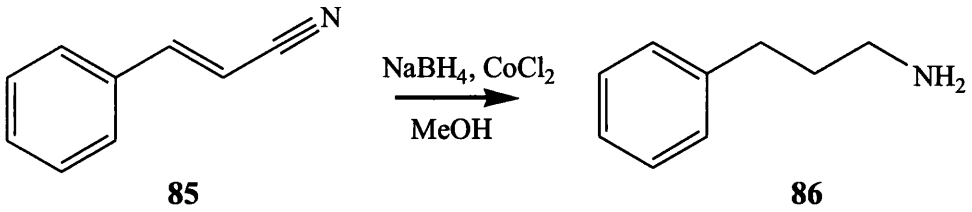
85 **86**

Scheme 3.30: Reduction of 85 with lithium aluminium hydride in Et_2O to give the amine 86.

Cinnamonitrile (**85**, 0.570 g, 4.41 mmol) was dissolved in dry diethyl ether (25 mL, dried by stirring over calcium hydride and subsequent distillation) in a 50 mL round-bottom flask fitted with a condenser, which had been flushed out with argon. Lithium aluminium hydride (5.7 mL of a 2.3 mol dm^{-3} suspension in THF, 12.9 mmol) was added slowly through the condenser. The resultant green solution was refluxed at 50 °C for three hours, until TLC monitoring indicated full consumption of starting material had occurred. The mixture was cooled to room temperature and water was added dropwise until the violent reaction ceased. The mixture was filtered through celite and washed with dichloromethane. Aqueous HCl (2M, 35 ml) was added and the mixture was extracted with dichloromethane (2 x 25 mL). GC analysis of the organic phase revealed no trace of cinnamonitrile. The aqueous phase (pH = 1) was basified with 2M aqueous NaOH until the pH was 14, at which point the amine separated out. The basified aqueous phase was extracted with dichloromethane (3 x 35 mL). The organic phase was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate and treated with decolourising charcoal (approx. 2 g, stirred at room temp. for 20 min.). Evaporation of the solvent and distillation under reduced pressure yielded the product **86** as an oil (bp 223 °C) with a slight green colour in 35 % yield (0.21 g, 1.54 mmol). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.12 (2H, s, D_2O exch., NH_2), 1.79 (2H, quintet, J = 8 Hz, $NH_2CH_2CH_2CH_2$), 2.65, 2.76 (2H, t, J = 8 Hz, $PhCH_2$, 2H, t, J = 8Hz, NH_2CH_2), 7.15-7.36 (5H, m, Ph*H*). δ_C (100 MHz, $CDCl_3$; Me_4Si) 33.7 ($PhCH_2$), 35.9 ($CH_2CH_2NH_2$), 42.2 (NH_2CH_2), 126.4 (phenyl *para*-CH), 128.5, 128.8 (phenyl *ortho*-CH, phenyl *meta*-CH), 142.6 (phenyl 1-*C*). *m/z* (ES^+) = 136.1122 ($[M+H]^+$ $C_9H_{14}N$ requires

136.1121). *m/z* (EI^+) = 118 (51 %), 91 (100 %), 77 ($[Ph]^+$ 29 %), 44 (38 %). *m/z* ($CI^+(NH_3)$), 136 ($[M+H]^+$ 100 %).

*3.11.13 Reduction of **85** with sodium borohydride/cobalt chloride.*

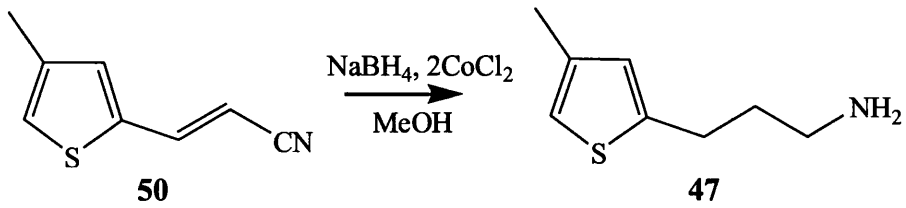


85 **86**

Scheme 3.31: Reduction of 85 with sodium borohydride ($NaBH_4$) and cobalt chloride ($CoCl_2$) in methanol to give the amine 86.

Cinnamonitrile (**85**, 0.516 g, 3.995 mmol) was dissolved in methanol (25 mL) in a 50 mL round-bottomed flask and anhydrous cobalt (II) chloride (1.04 g, 8.03 mmol) was added. The blue suspension was cooled in ice/water. Sodium borohydride (1.51 g, 40 mmol) was added gradually in small portions. The mixture released gas and a black precipitate was produced. The mixture was stirred overnight. Aqueous HCl (4M, 30 mL) was added, at which point the precipitate dissolved and a purple solution resulted. The methanol was removed under reduce pressure. The solution was extracted with diethyl ether (2 x 40 mL). The acidic purple aqueous solution (pH = 1) was basified with concentrated ammonia until a pH of 12 was obtained. The basified mixture was extracted with diethyl ether (4 x 50 mL). The organic phase was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulphate and treated twice with charcoal (approx. 2 g, stirred at room temp. for 20 min.). The solvent was removed under reduce pressure and the product was purified by reduced pressure distillation. The product **86** was isolated as a clear, colourless oil in 78 % yield (0.420 g, 3.10 mmol). The sample was identical in all respects to the product of the lithium aluminium hydride reduction and to the authentic sample.

3.11.14 *Reduction of **50** with sodium borohydride/cobalt chloride.*

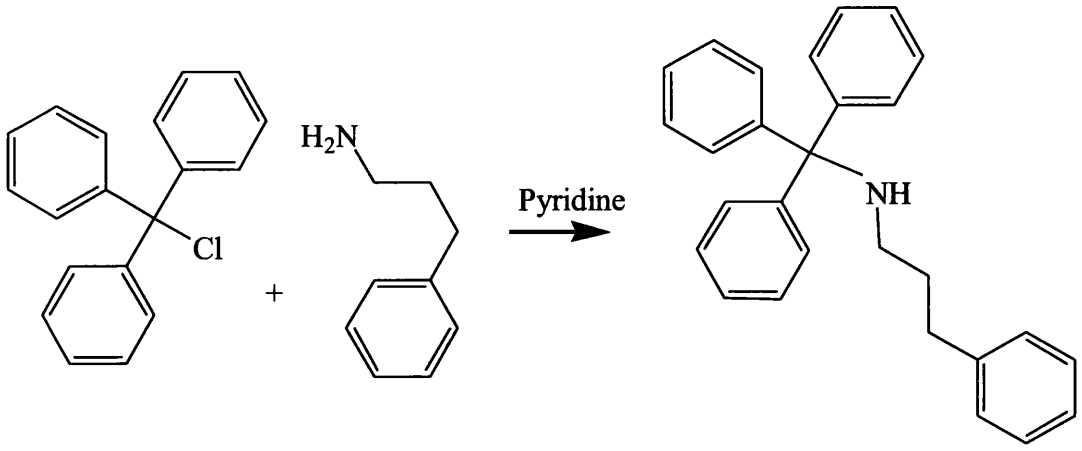


50 **47**

Scheme 3.32: Reduction of 50 with $NaBH_4$ and $CoCl_2$ in methanol to give the amine 47.

3-(4-Methyl-2-thienyl)acrylonitrile (**50**, 0.522 g, 3.50 mmol) was dissolved in methanol (25 mL) in a 50 mL round-bottomed flask and anhydrous cobalt (II) chloride (0.91 g, 7.00 mmol) was added. The blue suspension was cooled in ice/water. Sodium borohydride (0.52 g, 13.7 mmol) was added gradually in small portions. The mixture gave off gas and a black precipitate was produced. The mixture was stirred for 2 hours until TLC monitoring showed the absence of starting material. Hydrochloric acid (4M, 30 mL) was added, at which point the precipitate dissolved and a purple solution resulted. The methanol was removed under reduced pressure. The solution was extracted with diethyl ether (3 x 40 mL). The acidic purple solution (pH = 1) was basified with concentrated ammonia until a pH of 12 was obtained. The basified mixture was extracted with diethyl ether (4 x 50 mL). The organic phase was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and treated twice with charcoal (approx. 2 g, stirred at room temp. for 20 min.). The solvent was removed under reduced pressure and the product was purified by distillation under reduced pressure. The product **47** was isolated as a clear, colourless oil (bp 251 °C) in 63 % yield (0.342 g, 2.20 mmol). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.29 (2H, s, D_2O exch., NH_2), 1.73 (2H, quintet, J = 8 Hz, $NH_2CH_2CH_2$), 2.19 (3H, s, CH_3), 2.69, 2.77 (2H, t, J = 8 Hz, $NH_2CH_2CH_2CH_2$, 2H, t, J = 8 Hz, NH_2CH_2), 6.55 (1H, s, thienyl 3-*H*), 6.62 (1H, s, thienyl 5-*H*). δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.1 (CH_3), 27.8 ($CH_2CH_2CH_2NH_2$), 35.9 ($CH_2CH_2NH_2$), 41.9 (CH_2NH_2), 118.7 (thienyl 5-*C*H), 127.3 (thienyl 3-*C*H), 137.6 (thienyl 4-*C*), 145.2 (thienyl 2-*C*). *m/z* (ES^+) = 156.0843 ($[M+H]^+$ $C_8H_{14}NS$ requires 156.0841), *m/z* (EI^+) 155 ($[M]^+$ 17 %), 138 (100 %), 123 (63 %), 111 (72 %), 97 (27 %), 42 (32 %). *m/z* ($CI^+(NH_3)$) 173 ($[M+NH_4]^+$, 5 %), 156 ($[M+H]^+$ 100 %), 124 (15 %), 52 (90 %).

3.11.15 *Synthesis of N-(3-phenyl-1-propyl)tritylamine (87).*



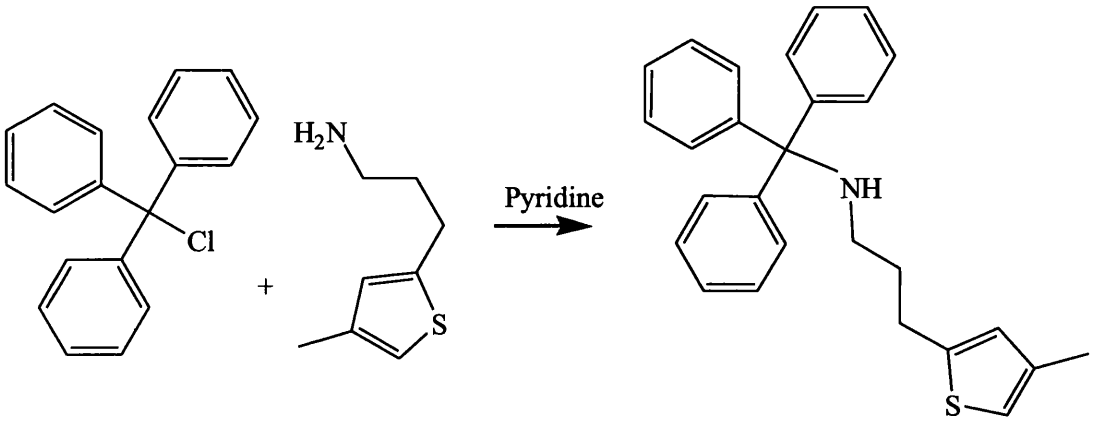
88 **86** **87**

Scheme 3.33: Test protection of 86 as the trityl derivative 87 by reaction with trityl chloride (88) in pyridine.

A solution of triphenylmethyl chloride (**88**, 1.11 g, 3.99 mmol) in dry, distilled pyridine (10 mL) was added slowly to a solution of 3-phenyl-1-propylamine (**86**, 0.546 g, 4.04 mmol) in dry distilled pyridine (10 mL) in a 50 mL round-bottomed flask cooled in ice/water. The reaction mixture was stirred for 24 hours. Ice water was added to the reaction mixture and a white solid precipitated out immediately. The solid was removed from the mixture by Büchner filtration and washed with water. The solid was dissolved in chloroform (25 mL) and the solution formed was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (alumina, 10% ethyl acetate/hexane). The product **87** was recrystallised from chloroform and isolated as white crystals (mp 84.6-86.0 °C) in 53% yield (0.798 g, 2.12 mmol). Anal. Found: C 88.77, H 7.18, N 3.67 %. Calc. for $C_{28}H_{27}N$: C 89.08, H 7.21, N 3.71 %. δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.45 (1H, s, D_2O exch. N*H*), 1.73 (2 H, quintet, J = 8 Hz, CH_2CH_2NH), 2.15 (2H, t, J = 8 Hz, CH_2NH), 2.60 (2H, t, J = 8 Hz, $CH_2CH_2CH_2NH$), 7.0-7.5 (20H, m, Ph*H*). δ_C (100 MHz; $CDCl_3$; Me_4Si) 33.0 ($CH_2CH_2CH_2NH$), 34.2 (CH_2CH_2NH), 43.8 (CH_2NH), 71.3 (CPh_3), 126.1, 126.6 (propylphenyl *para*-*C*H, trityl phenyl *para*-*C*H), 128.2 (trityl phenyl *ortho*-*C*H), 128.7 (propylphenyl *ortho*-*C*H, propylphenyl *meta*-*C*H,), 129.1 (trityl phenyl *meta*-*C*H), 142.8 (phenyl 1-*C*), 146.7 (trityl phenyl 1-*C*). *m/z* (ES^+) = 378.2217 ($[M+H]^+$ $C_{28}H_{28}N$ requires 378.2216). *m/z* (EI^+) = 300 ($[M-Ph]^+$ 48 %), 243 ($[CPh_3]^+$ 100 %), 165 (76 %), 117

([Ph{CH_2}$_3$]$^+$ 44 %), 91 ([$PhCH_2$]$^+$ 53 %), 77 ([Ph]$^+$ 22 %). *m/z* ($CI^+(NH_3)$) = 378 ([M+H]$^+$, 100 %), 300 ([M-Ph]$^+$ 70 %), 243 ([CPh_3]$^+$ 90 %), 136 (100 %).

3.11.16 Synthesis of N-[3-(4-methyl-2-thienyl)-1-propyl]tritylamine (60).



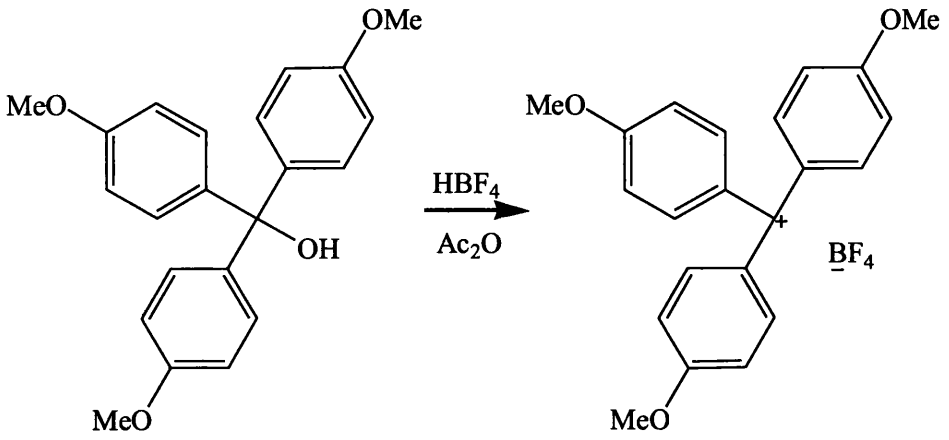
88 **47** **60**

Scheme 3.34: Protection of 47 as the trityl derivative 60 by reaction with 88 in pyridine.

A solution of triphenylmethyl chloride (**88**, 0.528 g, 1.89 mmol) in dry, distilled pyridine (10 mL) was added slowly to a solution of 3-(4-methyl-2-thienyl)-1-propylamine (**47**, 0.278 g, 1.89 mmol) in dry distilled pyridine (10 mL) in a 50 mL round-bottomed flask cooled in ice/water. The reaction mixture was stirred for 24 hours. Ice water was added to the reaction mixture and a white solid precipitated out immediately. The solid was removed from the mixture by Büchner filtration and washed with water. The solid was dissolved in chloroform (50 mL) and the solution formed was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (alumina, 10% ethyl acetate/hexane). The product **60** was recrystallised from chloroform and isolated as white crystals (mp 77.8-78.5 °C) in 54% yield (0.381 g, 0.960 mmol). Anal. Found: C 81.21, H 6.74, N 3.54 %. Calc. for $C_{27}H_{27}NS$: C 81.60, H 6.85, N 3.52 %. δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.45 (1H, s, D_2O exch. N*H*), 1.77 (2H, quintet, *J* = 8 Hz, CH_2CH_2NH), 2.05-2.20 (5H, m, CH_3 + CH_2NH), 2.74 (2H, t, *J* = 8 Hz, $CH_2CH_2CH_2NH$), 6.45 (1H, s, thienyl 3-*H*), 6.59 (1H, s, thienyl 5-*H*), 7.12 (3H, t, *J* = 7 Hz, phenyl *para-H*), 7.20 (6H, t, *J* = 7 Hz, phenyl *meta-H*), 7.37 (6H, t, *J* = 7 Hz, phenyl *ortho-H*). δ_C (100 MHz, $CDCl_3$; Me_4Si) 16.2 (CH_3), 28.4 ($CH_2CH_2CH_2NH$), 33.2 (CH_2CH_2NH), 43.4 (CH_2NH), 71.27 (CPh_3), 118.4 (thienyl 5-*C*H), 126.7, 127.0 (thienyl 3-*C*H, phenyl *para-C*H), 128.2 (phenyl *ortho-C*H), 129.1

(phenyl *meta*-*C*H), 137.7 (thienyl 4-*C*), 145.6 (thienyl 2-*C*), 146.6 (phenyl 1-*C*). *m/z* (ES^+) = 398.1936 ($[M+H]^+$ $C_{27}H_{28}NS$ requires 398.1937). *m/z* (EI^+) 320 ($[M-Ph]^+$ 8 %), 243 ($[M-Ph_2]^+$ 100 %), 165 (63 %), 138 (33 %), 111 (32 %), 77 ($[Ph]^+$ 14 %). *m/z* ($CI^+(NH_3)$) = 398 ($[M+H]^+$, 100 %), 320 ($[M-Ph]^+$, 26 %), 243 ($[M-Ph_2]^+$ 100 %), 156 (73 %).

3.11.17 Synthesis of 4,4',4''-trimethoxytrityl tetrafluoroborate (90).



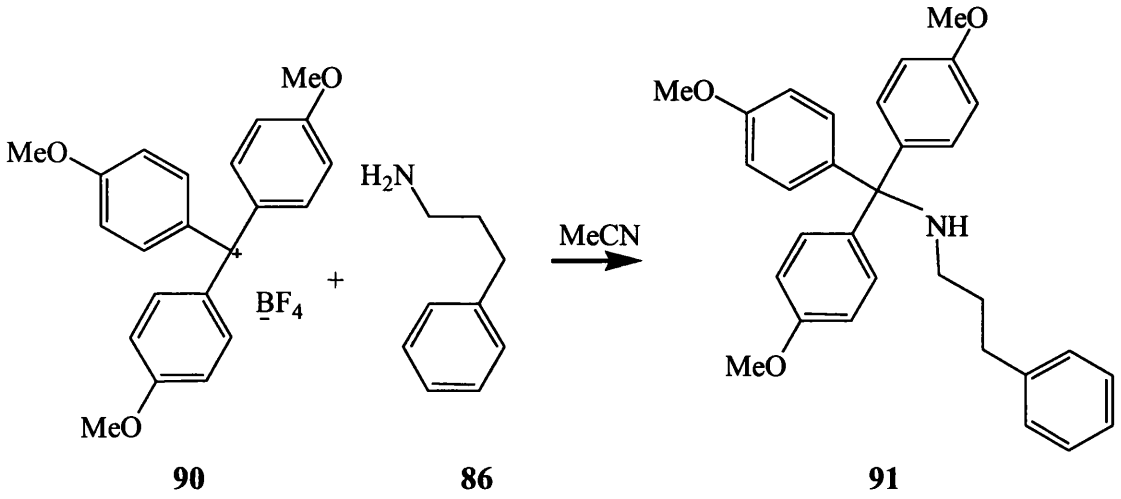
89 **90**

Scheme 3.35: Reaction of 4,4',4''-trimethoxytrityl alcohol (89) with fluoroboric acid to form 90.

4,4',4''-Trimethoxytrityl alcohol (**89**, 4.831 g, 13.8 mmol) was dissolved in freshly distilled acetic anhydride (30 mL) in a 100 mL round-bottomed flask. The colourless solution was cooled in ice/water. Aqueous tetrafluoroboric acid (18 mL of a 50% aqueous solution) was added dropwise *via* syringe over the course of 1 hour. The solution turned purple. After a further hour of stirring diethyl ether (50 mL) was added, and over the next hour the product, 4,4',4''-trimethoxytrityl tetrafluoroborate precipitated out as a purple solid. The product was collected by Büchner filtration with washings with diethyl ether, in which the alcohol starting material is soluble but the fluoroborate salt is not. The crystals were pumped overnight with an oil pump until the weight was constant. The product **90** was isolated as purple crystals (mp 177.7 -179.1 °C, lit.[104] 176-178 °C) in 94% yield (5.45 g, 12.9 mmol). δ_H (400 MHz; acetone-d^6; Me_4Si) 4.15 (9H, s, OCH_3), 7.45 (6H, d, J = 9 Hz, anisyl *meta*-*H*), 7.73 (6H, d, J = 9 Hz, anisyl *ortho*-*H*). δ_C (100 MHz, acetone-d^6; Me_4Si) 58.0 (OCH_3), 117.6 (anisyl *ortho*-*C*H), 133.7 (anisyl 4-*C*), 144.5 (anisyl *meta*-*C*H), 171.80 (anisyl 1-*C*OMe). δ_F (376 MHz, acetone-d^6) 25.8. *m/z* (ES^+) =

333.1486 ([M-BF_4]$^+$ $C_{22}H_{21}O_3$ requires 333.1485), *m/z* (ES^+) = 333 ([M-BF_4]$^+$ 100 %), 99 (58 %), 87 (32 %), 65 (100 %).

3.11.18 Synthesis of N-(3-phenylpropyl)-4,4',4''-trimethoxytritylamine (91).



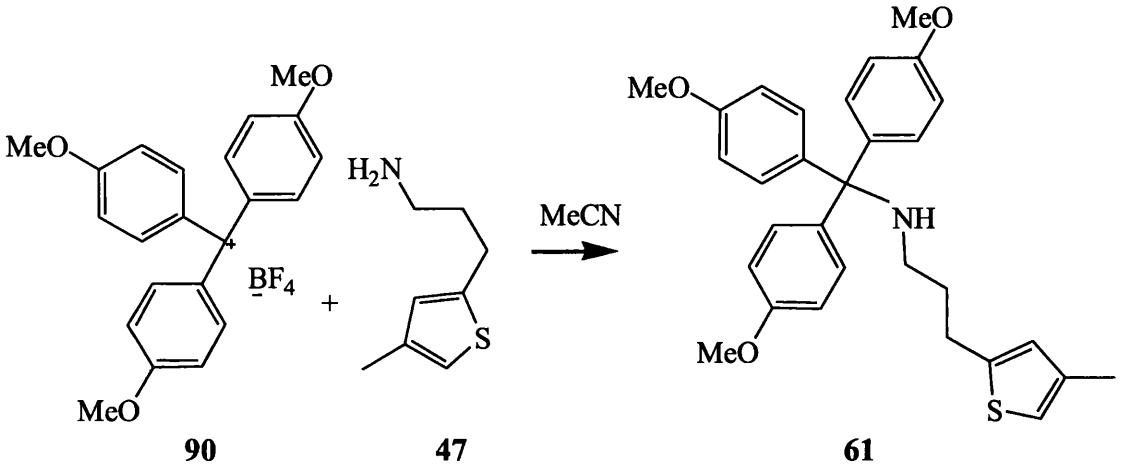
90 **86** **91**

Scheme 3.36: Protection of 86 as the TMT derivative 91 by reaction with 90 in acetonitrile.

4,4',4''-Trimethoxytrityl tetrafluoroborate (**90**, 0.624 g, 1.49 mmol) was dissolved in dry distilled acetonitrile (10 mL) in a 50 mL round-bottomed flask that had been flushed with argon. 3-Phenyl-1-propylamine (**86**, 0.437 g, 3.23 mmol) was added dropwise to the purple solution over the period of 10 minutes. Upon addition of all of the amine the solution turned light green. The solution was stirred for 1 hour, after which the stirrer was removed and the solvent was removed under reduced pressure. Sodium hydroxide (2M, 30 mL) was added to the residue, and the resulting mixture was extracted with diethyl ether (6 x 25 mL). The organic phase was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was isolated by column chromatography (alumina, 30/70/1 ethyl acetate/hexane/triethylamine). The product **91** was isolated as an off-white gum in 54 % yield (0.374 g, 0.800 mmol). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.72 (3H, D_2O exch. gives 2H, quintet, J = 8 Hz, CH_2CH_2NH + NH), 2.12 (2H, t, J = 8 Hz, CH_2NH), 2.55 (2H, t, J = 8 Hz, $PhCH_2$), 3.65 (9H, s, OCH_3), 6.68 (6H, d, J = 7 Hz, anisyl *ortho-H*), 7.00-7.10 (3H, m, phenyl *ortho-H* + *para-H*), 7.14 (2H, t, J = 7 Hz, phenyl *meta-H*), 7.23 (6H, d, J = 7 Hz, anisyl *meta-H*). δ_C (100 MHz, $CDCl_3$; Me_4Si) 33.0 ($PhCH_2$), 34.3 (CH_2CH_2NH), 43.7 (CH_2NH), 55.6 (OCH_3), 69.7 ($NHCAr_3$), 113.5 (anisyl *ortho-C*H), 126.1 (phenyl

para-CH), 128.7, 128.8 (phenyl *ortho*-CH, phenyl *meta*-CH), 130.1 (anisyl *meta*-CH), 140.2 (anisyl *para*-C), 143.0 (phenyl 1-C), 158.1 (anisyl 1-COMe). *m/z* (EI^+) = 467.2448 ($[M]^+$ $C_{31}H_{33}O_3N$ requires 467.2455). *m/z* (EI^+) = 467 ($[M]^+$ 100%), 360 ($[M\text{-}C_6H_4OMe]^+$ 36 %), 333 ($[C(C_6H_4OMe)_3]^+$ 100%), 134 ($[M\text{-}C(C_6H_4OMe)_3]^+$ 15 %), 91 ($[PhCH_2]^+$ 100%), 77 ($[Ph]^+$ 57 %).

3.11.19 *Synthesis of N-[3-(4-methyl-2-thienyl)-1-propyl]-4,4',4''-trimethoxytritylamine (61)*



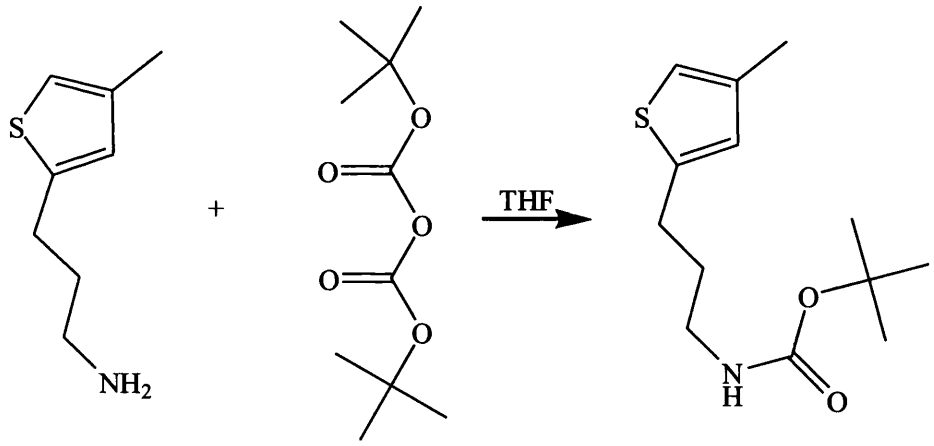
90 **47** **61**

Scheme 3.37: Protection of 47 as the TMT derivative 61 by reaction with 90 in acetonitrile.

4,4',4''-Trimethoxytrityl tetrafluoroborate (**90**, 0.295 g, 0.701 mmol) was dissolved in dry distilled acetonitrile (10 mL) in a 50 mL round-bottomed flask that had been flushed with argon. 3-(4-Methyl-2-thienyl)-1-propylamine (**47**, 0.239 g, 1.67 mmol) was added dropwise to the purple solution over a period of 10 min. Upon addition of all of the amine the solution turned light green. The solution was stirred for 1 hour, after which the stirrer was removed (to prevent bumping in the rotary evaporator) and the solvent was removed under reduced pressure. Sodium hydroxide (2M, 20 mL) was added to the residue, and the resulting mixture was extracted with diethyl ether (6 x 25 mL). The organic phase was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was isolated by column chromatography (alumina, 30/70/1 ethyl acetate/hexane/triethylamine). The product **61** was isolated as an off-white gum in 55% yield (0.187 g, 0.383 mmol). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.72 (2H, quintet, J = 8 Hz, CH_2CH_2NH), 2.13 (6H, D_2O exch. gives 5H, m, CH_3 + CH_2NH + N*H*), 2.72 (2H, t, $CH_2CH_2CH_2NH$), 3.70 (9H, s, OCH_3),

6.42 (1H, s, thienyl 3-*H*), 6.54 (1H, s, thienyl 5-*H*), 6.71 (6H, d, J = 7 Hz, anisyl *ortho-H*), 7.25 (6H, d, J = 7 Hz, anisyl *meta-H*). δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.2 (CH_3), 28.5 ($CH_2CH_2CH_2NH$), 33.2 (CH_2CH_2NH), 43.4 (CH_2NH), 55.7 (OCH_3), 69.7 ($NHCAr_3$), 113.4 (anisyl *ortho-C*H), 118.4 (thienyl 5-*C*H), 127.0 (thienyl 3-*C*H), 130.0 (anisyl *meta-C*H), 137.7 (thienyl 4-*C*), 139.4 (anisyl *para-C*), 145.7 (thienyl 2-*C*), 158.1 (phenyl 1-*C*OMe). *m/z* (EI^+) = 486.2088 ($[M-H]^+$ $C_{30}H_{32}O_3NS$ requires 486.2097). *m/z* (EI^+) = 486 ($[M-H]^+$ 15 %), 380 ($[M-C_6H_4OMe]^+$ 28 %), 333 ($[C(C_6H_4OMe)_3]^+$ 100%), 111 (58 %), 77 ($[Ph]^+$ 34 %).

3.11.20 *Synthesis of [3-(4-methyl-2-thienyl)-1-propyl]carbamic acid tert-butyl ester (63).*



47 **62** **63**

Scheme 3.38: Protection of 47 as the Boc derivative 63 by reaction with 62 in THF.

Di-*tert*-butyl dicarbonate (**62**, 0.490 g, 2.24 mmol) was dissolved in dry, distilled THF (10 mL) in a 50 mL round-bottomed flask. 3-(4-Methyl-2-thienyl)-1-propylamine (**47**, 0.358 g, 2.30 mmol) was added dropwise and the solution was stirred overnight. The stirrer was removed from the solution and then the solvent was removed under reduced pressure. The residue was dissolved in 60 mL ethyl acetate, and the resulting solution was washed with saturated aqueous sodium bicarbonate solution (40 mL), 5% aqueous potassium hydrogen sulfate solution (40 mL) and water (40 mL) and then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (alumina, 5% ethyl acetate/hexane). The product **63** was isolated as a mobile light green oil in 93% yield (0.550 g, 2.15 mmol).

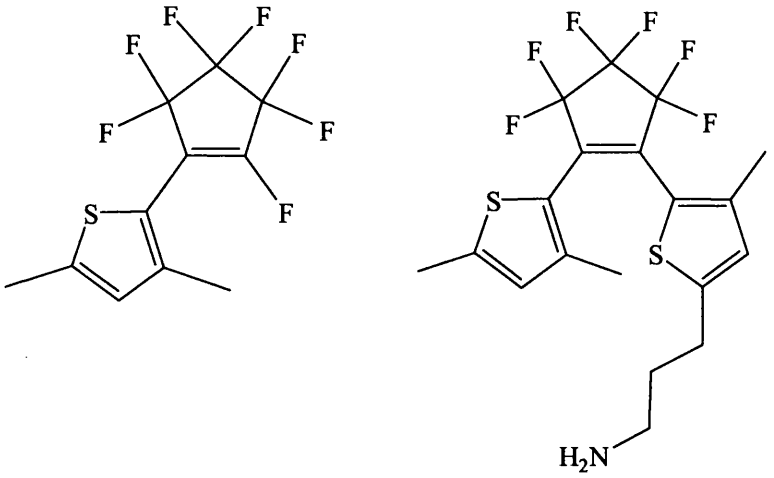
ν_{max} (film) /cm^{-1} 1654 (C=O). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.34 (9H, s, C(C*H*$_3$)$_3$), 1.71 (2H, quintet, *J* = 8 Hz, C*H*$_2$CH$_2$NH), 2.12 (3H, s, C*H*$_3$), 2.66 (2H, t, *J* = 8 Hz C*H*$_2$CH$_2$CH$_2$NH), 3.04 (2H, m, C*H*$_2$NH), 4.51 (1H, s, D_2O Ex., N*H*), 6.50 (1H, s, thienyl 3-*H*), 6.58 (1H, s, thienyl 5-*H*). δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.1 (*C*H$_3$), 27.7 (*C*H$_2$CH$_2$CH$_2$NH), 28.8 (C(*C*H$_3$)$_3$), 32.3 (*C*H$_2$CH$_2$NH), 40.4 (*C*H$_2$NH), 79.5 (*C*(CH$_3$)$_3$), 118.6 (thienyl 5-*C*H), 127.3 (thienyl 3-*C*H), 137.8 (thienyl 4-*C*), 144.6 (thienyl 2-*C*), 156.4 (*C*=O). *m/z* (ES$^+$) = 256.1367 ([M+H]$^+$ $C_{13}H_{22}O_2NS$ requires 126.1366). *m/z* (EI$^+$) = 199 ([M-C(CH$_3$)$_3$]$^+$ 36 %), 138 ([M-NHBoc]$^+$ 91 %), 125 (83 %), 111 (100 %), 57 ([C(CH$_3$)$_3$]$^+$ 93%). *m/z* (CI$^+$(NH$_3$)) = 273 ([M+NH$_4$]$^+$ 100 %), 256 ([M+H]$^+$, 32 %), 217 (26 %), 200 (16 %), 156 (21 %).

Chapter Four:

Synthesis of an unsymmetrical photochromic molecule with an amine linker.

4.1. Introduction.

As reported in Chapter 3 it was discovered that, although the synthesis of 3-(4-methyl-2-thienyl)-1-propylamine (**47**) and the subsequent protection reactions were successful, the conversion reactions of the protected amines to the corresponding protected photochromic amines *via* lithiation and subsequent reaction with **46** (**figure 4.1**) was unsuccessful. Therefore that route to the target molecule (**45**, **Figure 4.1**) was abandoned.



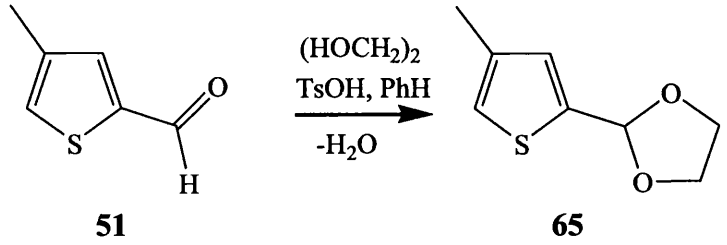
46 **45**

Figure 4.1: The monosubstituted perfluorocyclopentene 46 and the proposed linkable photochromic molecule 45.

The alternative route to **45**, discussed in Section 1.12, involved lithiation of a suitably protected form of 4-methyl-2-thiophenecarboxaldehyde (**51**) and its reaction with **46**, followed by subsequent functionalisation to give **45.**

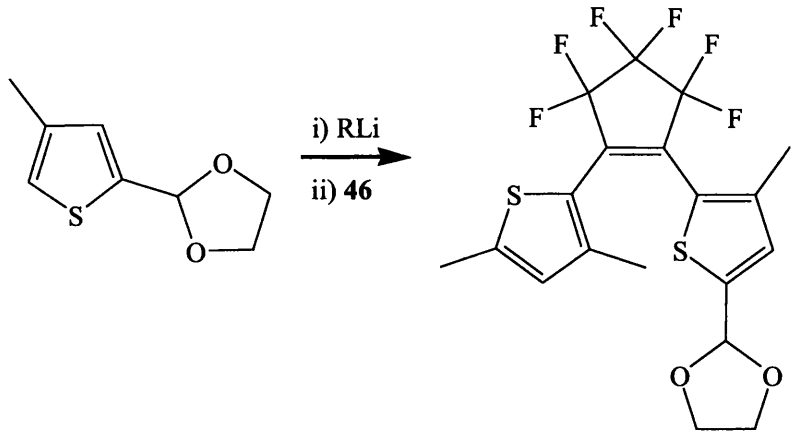
As reported in Chapter 2, **51** was synthesised with high selectivity and in high yield by the lithiation of **38** with **69** and subsequent reaction DMF. It was decided to protect **51** as the cyclic acetal **65**, which is a common reaction[115-117] as shown in **Scheme 4.1**

It was hoped that reaction with **46** would give the photochromic acetal **66**, as shown in **Scheme 4.2**. If this reaction was successful, **66** could be deprotected to form the corresponding aldehyde, which could be converted to **45** in a similar fashion to the successful conversion of **51** to **47**, as reported in Chapter 3.



51 **65**

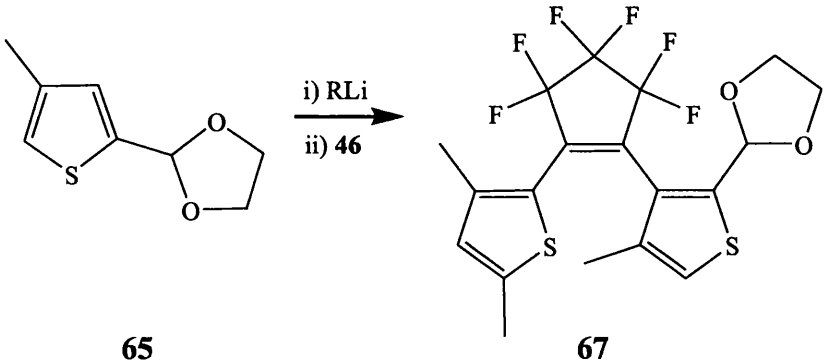
Scheme 4.1: Proposed protection of aldehyde 51 by reaction with ethylene glycol to give the cyclic acetal 65.



65 **66**

Scheme 4.2: Proposed lithiation of the cyclic acetal 65 (a protected form of aldehyde 51) and reaction with 46 to give the photochromic acetal 66.

It was suspected, however, that the cyclic acetal group might be able to direct lithiation to the 3-position on the thiophene ring of **65**, and that reaction with **46** could therefore lead to the formation of the unwanted by-product **67**, as shown in **Scheme 4.3**, so detailed structural analysis would be necessary.

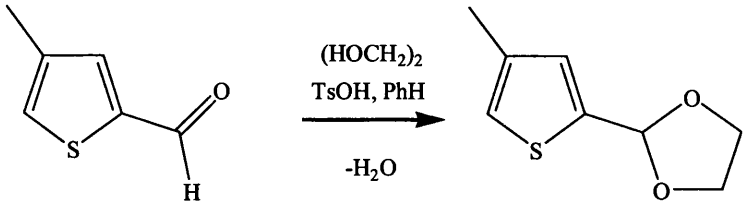


65 **67**

Scheme 4.3: Undesirable possible reaction of 65 with 46 (cf. Scheme 1.37) involving lithiation of 65 in the 3-position of the thiophene ring and reaction with 46 to give the unwanted product 67.

4.2. Synthesis of 2-(4-methyl-2-thienyl)-[1,3]dioxolane (65).

The starting material, **51**, was synthesised from **38** as reported in Chapter 2. Compound **51** was dissolved in benzene along with ethylene glycol and *para*-toluenesulfonic acid (TsOH) and the mixture was refluxed using a Dean & Stark trap. Aqueous workup with saturated sodium hydrogen carbonate solution followed by distillation afforded **65** as a clear colourless oil in 85 % yield. The reaction is shown in **Scheme 4.4**.



51 **65**

Scheme 4.4: Protection of aldehyde 51 by reaction with ethylene glycol to give the cyclic acetal 65.

^{1}H NMR analysis showed that the peak corresponding to the aldehyde proton of **51** had disappeared and that peaks corresponding to what would be expected from the cyclic acetal group were present. ^{13}C NMR analysis correlated similarly with expectations. High-resolution MS analysis (ES^+) showed a peak at m/z = 171.0475 (calculated value for the protonated form of **65**; 171.0474). More detailed characterisation data can be found in the experimental section.

Initially, GC analysis of the purified product showed that it was 97.6 % pure. The impurity was identified as the aldehyde starting material **51**. Over the course of several days monitoring of the sample by GC analysis showed that the sample was slowly decomposing to form **51** and ethylene glycol, probably due to the presence of water from the air. Reactions of **65** were therefore always carried out when **65** had been freshly prepared. In conclusion, the novel compound **65** has been successfully synthesised by the reaction of **51** with ethylene glycol in the presence of TsOH.

4.3. Synthesis of 2-{5-[2-(3,5-dimethyl-2-thienyl)perfluorocyclopent-1-enyl]-4-methyl-2-thienyl}-[1,3]dioxolane.

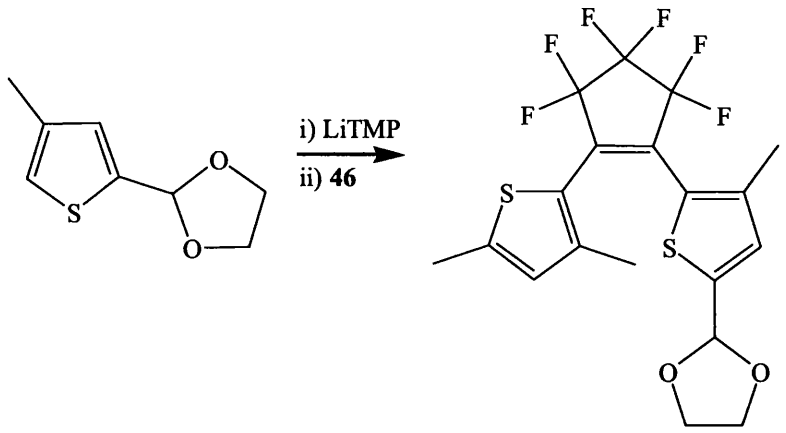
Initially, small-scale reactions were carried out involving lithiation of **65** with several different organolithium reagents and reaction with **46**.

Lithiation of **65** at 0 °C with *n*-butyllithium followed by reaction with **46** and by aqueous workup afforded a reaction mixture that was quite complex. GC analysis showed traces of both starting materials (**65** and **46**) and several smaller peaks, but the mixture was primarily composed of one large peak that had not previously been seen. GC/MS analysis showed that the major peak had a molecular mass of 454, which was consistent with both the desired product **66** and the unwanted isomer **67**. Immediate addition of aqueous HCl and THF to the mixture, stirring overnight followed by basic workup afforded a similarly complex mixture dominated by a further new peak. GC/MS analysis showed this new peak to have a mass of 410, which was consistent with the deprotected photochromic aldehyde **64**. These results indicated that the product or its regioisomer had been successfully formed.

Lithiation at -78 °C with *tert*-butyllithium gave a similar result but the reaction mixture was much cleaner. This effect was thought to be due to the low temperature eliminating any unwanted side reactions.

Lithiation at -78 °C with lithium 2,2,6,6-tetramethylpiperidide (**69**) afforded a very clean reaction mixture with very little starting material present. This reaction was scaled up in order for the product to be isolated, and after aqueous workup using saturated NH_4Cl, purification by column chromatography and recrystallisation the product **66** was isolated as yellow crystals in 58 % yield. The successful reaction is shown in **Scheme 4.5**.

High-resolution MS analysis (ES^+) showed a peak at m/z = 455.0570 (calculated value for the protonated form of **66**, 455.0569). Microanalysis data correlated well with the calculated values for **66**. ^1H NMR analysis correlated well with predictions. The CH peak of the acetal-substituted thienyl ring had been shifted downfield in comparison with that of the dimethylthienyl ring, which gave a peak with a very similar chemical shift to that of the CH groups of the unmodified photochromic molecule **21**.



65 66

Scheme 4.5: Lithiation of cyclic acetal 65 and reaction with 46 to give the photochromic acetal 66.

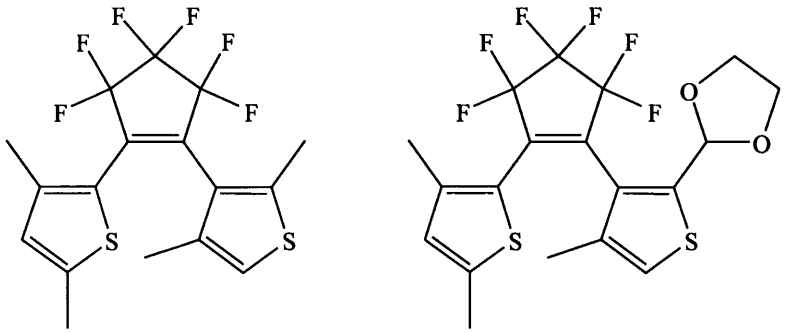
The ^{13}C NMR spectrum showed the expected CF splitting patterns corresponding to the carbons of the perfluorocyclopentene ring. The quaternary carbons of the thienyl rings each appeared as pairs of peaks consisting of the peaks corresponding to the carbon of the unmodified dimethylthienyl ring and the analogous carbon of the modified acetal-substituted thienyl ring, which had each been shifted slightly due to the modification of the structure. The ^{13}C NMR spectrum correlated well with predictions for **66**. Both NMR spectra looked like combinations of the spectra of the two starting materials **65** and **46**. More detailed characterisation data can be found in the experimental section.

As mentioned previously, it was necessary to confirm the structure of **66** beyond reasonable doubt due to the possibility of the formation of the unwanted by-product **67**. The MS analysis and microanalysis would have given the same results for both isomers **66** and **67**, and the predicted values for the NMR spectra of the two isomers were not appreciably different, so the NMR analysis was not conclusive. It was therefore necessary to confirm the structure of **66** by other means.

As has previously been discussed in Section 1.12, the position at which the thiophene ring is substituted onto the perfluorocyclopentene ring has been shown to have an effect on the photochromic characteristics of dithienylperfluorocyclopentenes. In their 1995 paper, Uchida and Irie synthesised the photochromic molecule **68**, which is a regioisomer of **21** and structurally analogous to the unwanted by-product **67**. Both of these molecules are shown in **Figure 4.2.**

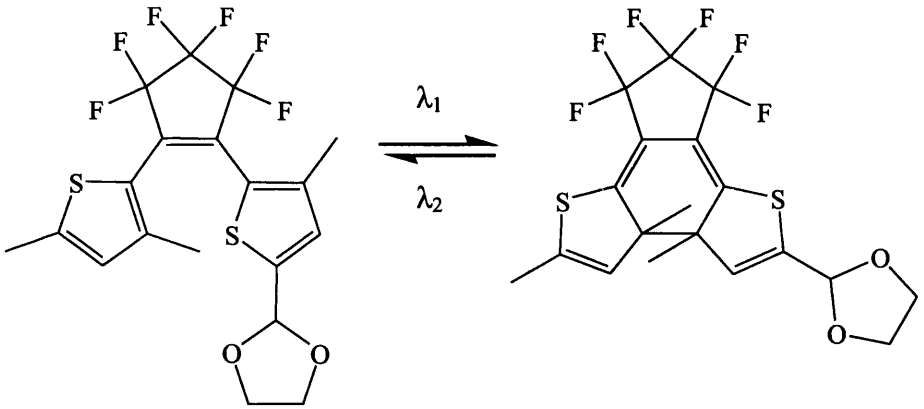
It was reported that molecule **68** had an A-form λ_{max} of 312 nm and a B-form λ_{max} of 469 nm in hexane, as opposed to the values given for **21** (A-form λ_{max} = 336 nm, B-form

λ_{max} = 425 nm in hexane, confirmed in Chapter 3 of this work). As the cyclic acetal group was not expected to affect the conjugation of the product it was expected that **66** would have very similar or identical spectroscopic properties to **21**, and that **67** would have very similar or identical spectroscopic properties to **68**. With this in mind the photochromic reaction of **66** **(Scheme 4.6)** was investigated.



68 **67**

Figure 4.2: The similarity of the structure of the photochromic molecule 68, reported by Uchida and Irie in 1995[50] to the unwanted by-product 67.



66 **92**

Scheme 4.6: The reversible photochromic conversion of the acetal 66 to the closed form 92.

UV-Vis Spectroscopic analysis of a colourless methanol solution of **66** (7.37 x 10^{-5} mol dm^{-3}) showed an absorption at λ = 339 nm, which correlated well with the measured value for **21** of λ = 345 nm in methanol. The solution was irradiated with UV light (λ = 366 nm) for 15 minutes, after which time it had developed a yellow colour (this can be seen in **Figure 4.3**). UV-Vis Spectroscopic analysis showed a pronounced decrease in the absorption at λ = 339 nm and the appearance of a new peak at λ = 437 nm which was ascribed to the closed form of **66** (i.e. **92**) correlating well with the measured value for the

closed form of **21** (i.e. **22**) of $\lambda = 437$ nm in hexane. The yellow solution lost its colour when placed in direct sunlight. This almost exact correlation with the photochromic behaviour of **21** was a very good indication that the desired product had indeed been formed. The colourless solution of **66** is shown in **Figure 4.3a** and the yellow solution of the photoconverted form **92** is shown in **Figure 4.3b**. The UV spectral change is shown in **Figure 4.4**.

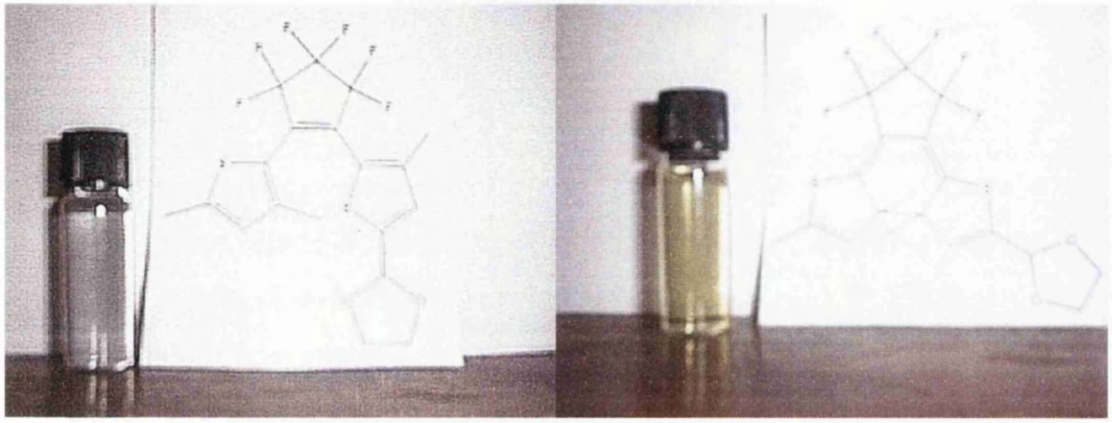


Figure 4.3a: The colourless solution of the A-form of the photochromic acetal (66)

Figure 4.3b: The yellow solution of the B-form of the photochromic acetal (92)

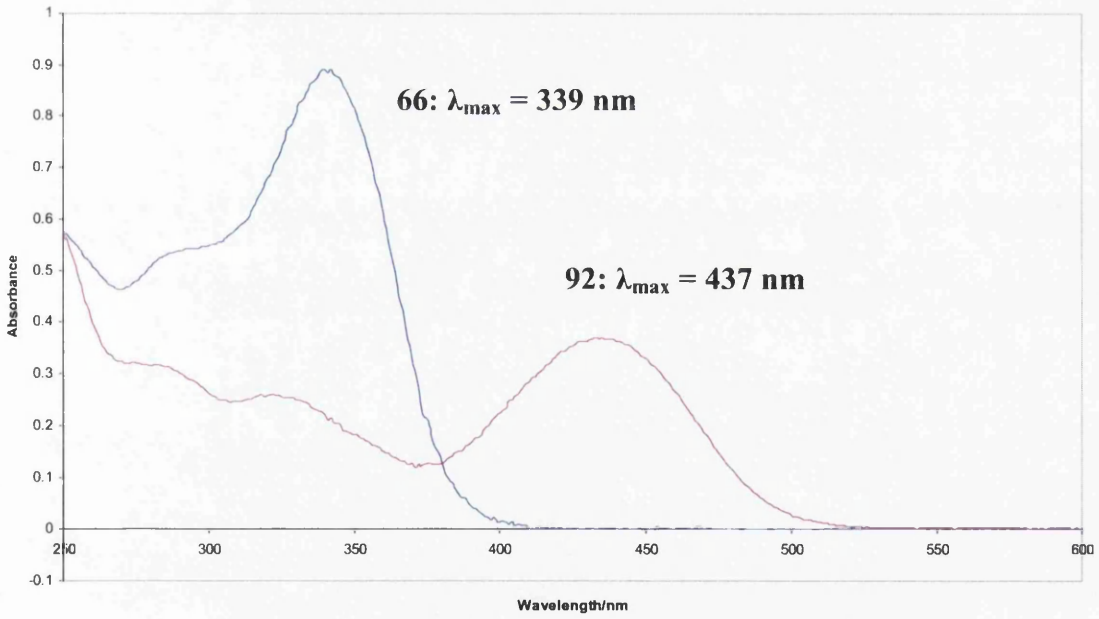


Figure 4.4: The UV-spectral change that accompanies the photochromic conversion of 66 to 92 (cf. Scheme 4.6). The colourless solution of open form 66 (cf. Figure 4.3a) exhibits an absorption at $\lambda = 339$ nm. Irradiation with UV light prompts the appearance of a yellow colour (cf. Figure 4.3b), which is accompanied by the reduction of the absorption at $\lambda = 339$ nm and the appearance of a new absorption at $\lambda = 437$ nm. This correlates well with the spectroscopic characteristics of the unmodified molecule 21 (cf. Figure 3.5).

The spectroscopic characteristics of the product showed that it was most likely the desired product **66**. In order to confirm beyond reasonable doubt that **66** had indeed been successfully synthesised the sample was subjected to X-ray crystallographic analysis and the structure of the product is shown in **Figure 4.5**. It is clear that substitution did indeed take place in the 5-position of the acetal **65,** and the product is confirmed as **66**. The full report of the crystallographic analysis can be found in Appendix 1.

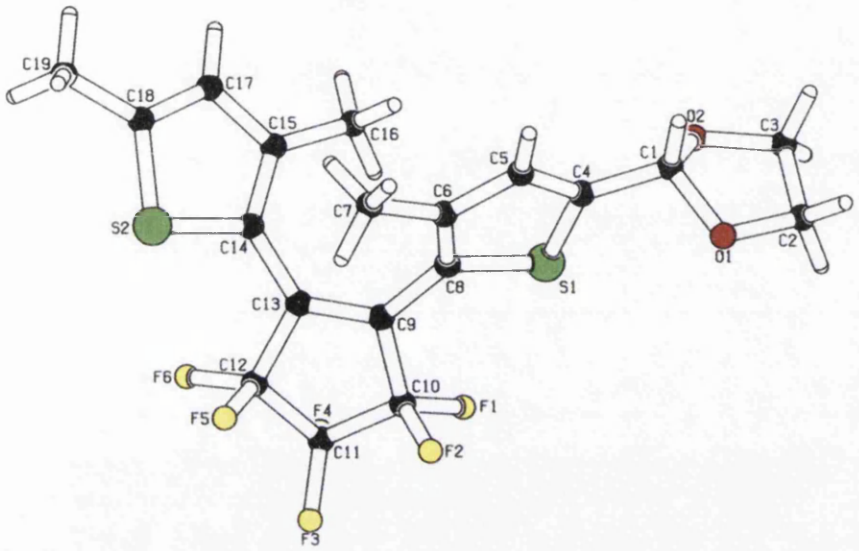
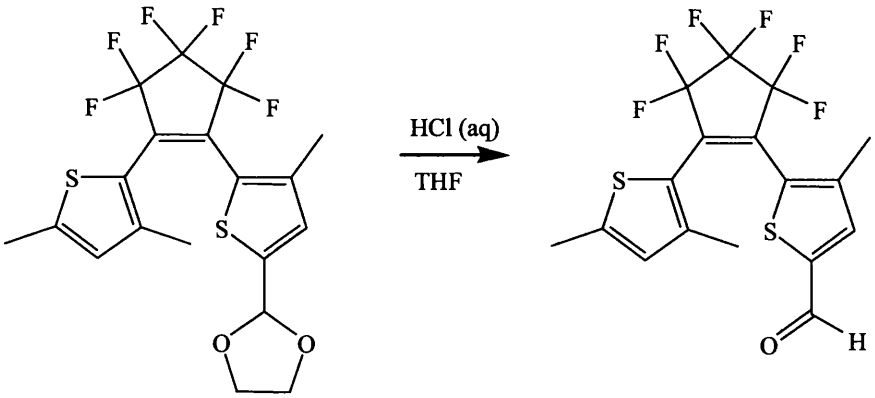


Figure 4.5: The structure of the photochromic acetal 66 as determined by X-Ray crystallographic analysis. The structure was determined by the EPSRC National Crystallography Service in the School of Chemistry, University of Southampton.

In conclusion, the novel compound **66**, which is a modified form of compound **21**, has been successfully synthesised by the lithiation of **65** and reaction with **46** and has been observed to undergo a reversible photochromic reaction that is very similar to that of **21**. The next stages of the synthesis of **45** involved the deprotection of **66** to form the aldehyde **64**, followed by funtionalisation of the aldehyde to the amine **45** (in a similar way to the functionalisation of **51** to form **47**, which was reported in Chapter 3).

4.4. Synthesis of 5-[2-(3,5-dimethyl-2-thienyl)perfluorocyclopent-1-enyl]-4-methyl-2-thiophenecarboxaldehyde (64).

Compound **66** was dissolved in THF and stirred overnight with 10% aqueous HCl. The reaction is shown in **Scheme 4.7**. After basic aqueous workup GC analysis showed the previously observed product peak that had given a molecular ion peak of $m/z = 410$ upon GC:MS analysis in an otherwise totally clean reaction mixture. Recrystallisation afforded the expected product **64** as yellow crystals in 92 % yield.

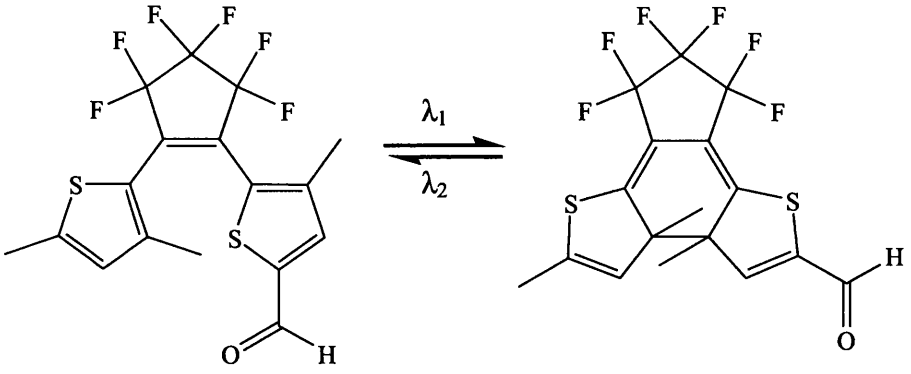


66 **64**

Scheme 4.7: The deprotection reaction of the acetal 66 with HCl to form the aldehyde 64.

^{1}H NMR analysis showed the expected peak corresponding to the aldehyde proton at $\delta = 9.79$ ppm. The signal corresponding to the ring CH proton of the thiophenecarboxaldehyde group showed a further downfield shift in comparison with the analogous peak in the spectrum of **66**, while the signal corresponding to the CH proton of the dimethylthiophene group was again in the same position as that in the spectrum of **21**. ^{13}C NMR analysis showed the expected carbonyl carbon peak at $\delta = 182.9$ ppm. The NMR spectra, again, looked like combinations of the spectra of **46** and the aldehyde **51**. The expected carbonyl signal was observed in the IR spectrum and microanalysis data correlated well with predicted values for **64**. High-resolution MS analysis (ES^+) showed a peak at m/z = 411.0307, which correlated exactly for the calculated value for the protonated form of **64**. More detailed characterisation data can be found in the experimental section.

The photochromic conversion of **64** to the closed form **93** is shown in **Scheme 4.8**.



64 **93**

Scheme 4.8: The reversible photochromic conversion of the aldehyde 64 to the closed form 93.

UV-Vis Spectroscopic analysis of a colourless methanol solution of **64** (7.26×10^{-5} mol dm^{-3}) showed an absorption at $\lambda = 349$ nm, which correlated well with the measured value for **21** of $\lambda = 345$ nm in methanol. Another peak was observed at $\lambda = 283$ nm which was not present in the spectra of **21** or **66** and was thought to be due to the presence of the carbonyl group. The solution was irradiated with UV light ($\lambda = 366$ nm) for 15 minutes, after which time it had developed a yellow colour (this can be seen in **Figure 4.6**). UV-Vis Spectroscopic analysis showed a decrease in the absorption at $\lambda = 349$ nm which was not as pronounced as that observed in the conversion of **66** and **21**, and the appearance of a new peak at $\lambda = 439$ nm, which was ascribed to the closed form of **64** (i.e. **93**), correlating well with the measured value for the closed form of **21** (**22**) of $\lambda = 437$ nm. The yellow solution lost its colour when placed in direct sunlight. The colourless solution of **64** is shown in **Figure 4.6a** and the yellow solution of the photoconverted form **93** is shown in **Figure 4.6b**. The UV spectral change is shown in **Figure 4.7**.

In conclusion, the novel compound **64** has been synthesised *via* the successful deprotection reaction of **66** with HCl, and has been shown to be photochromic.

The next stage of the synthesis involved the conversion of **64** to the corresponding acrylonitrile compound using the Horner/Wadsworth/Emmons reaction (previously used to convert **51** to **50**, as is reported in Chapter 3).

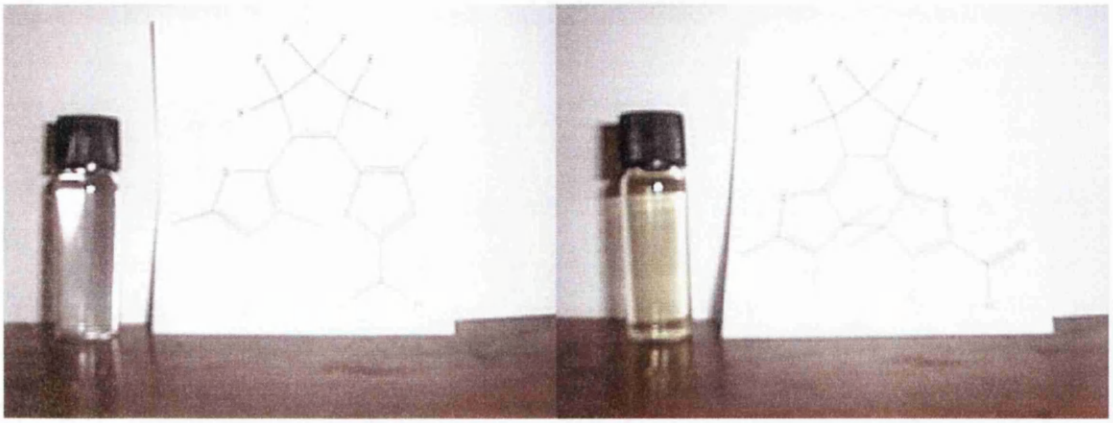


Figure 4.6a: The colourless solution of the A-form of the photochromic aldehyde (64)

Figure 4.6b: The yellow solution of the B-form of the photochromic aldehyde (93)

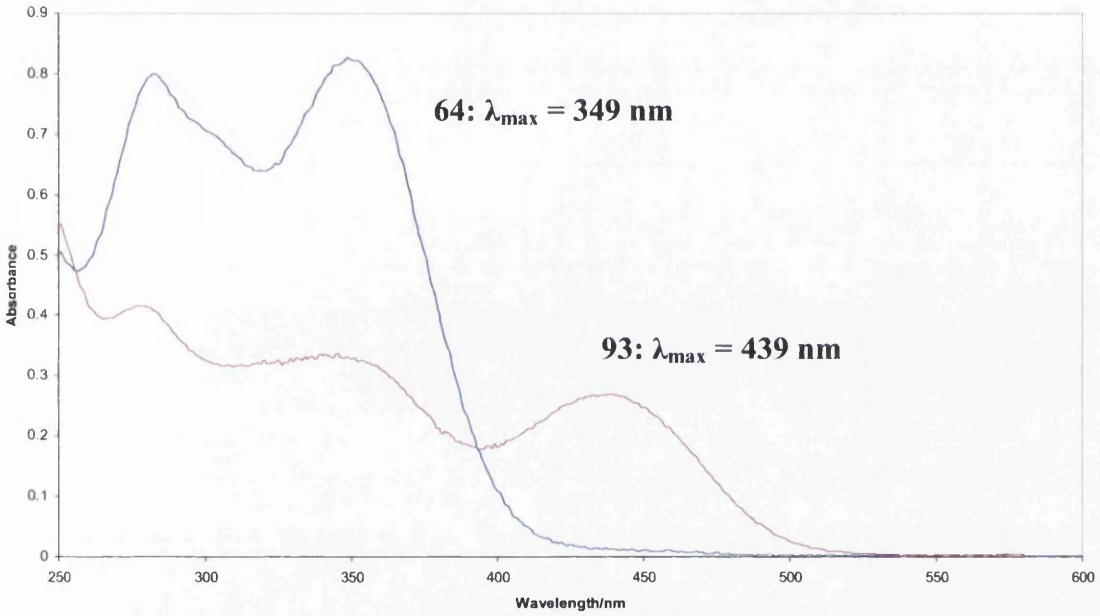
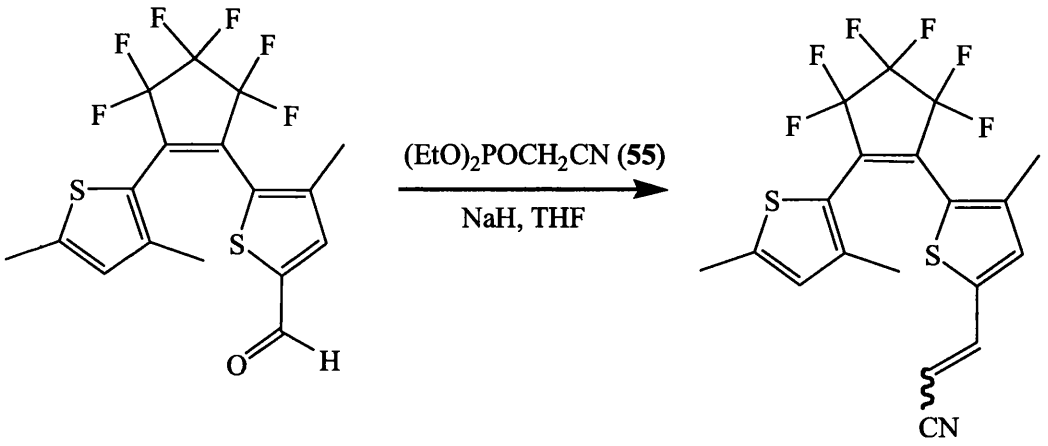


Figure 4.7: The UV-spectral change that accompanies the photochromic conversion of 64 to 93 (cf. Scheme 4.8). The colourless solution of open form 64 (cf. Figure 4.6a) exhibits an absorption at λ = 349 nm. Irradiation with UV light prompts the appearance of a yellow colour (cf. Figure 4.6b), which is accompanied by the reduction of the absorption at λ = 349 nm and the appearance of a new absorption at λ = 439 nm. This correlates well with the spectroscopic characteristics of the unmodified molecule 21 (cf. Figure 3.5).

4.5. Synthesis of 3-{5-[2-(3,5-dimethyl-2-thienyl)perfluorocyclopent-1-enyl]-4-methyl-2-thienyl}acrylonitrile (94).

Compound **64** was stirred overnight with diethylcyanomethylphosphonate (**55**) in THF in the presence of sodium hydride. Aqueous workup followed by purification by column chromatography and recrystallisation afforded **94** as yellow crystals in 89 % yield. GC analysis showed the product to be a mixture of *E*- and *Z*-isomers in a ratio of 5.5:1 respectively. The reaction is shown in **Scheme 4.9**.



64 **94**

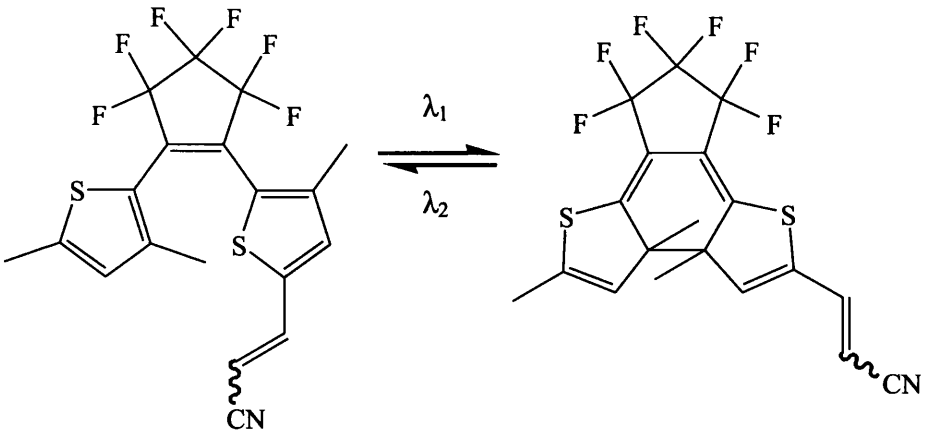
Scheme 4.9: The Horner/Wadsworth/Emmons reaction of 64 with 55 to form 94.

^{1}H NMR analysis correlated well with predictions. The expected sets of doublets corresponding to the olefinic protons of the two isomers of **94** were present in ratios of approximately 5.5:1, and the coupling constants suggested that the *E*-isomer was the major isomer present, as in the case of 3-(4-methyl-2-thienyl)acrylonitrile (**50**, cf. Chapter 3). The signal corresponding to the ring CH proton of the thienylacrylonitrile group showed an upfield shift in comparison with the analogous signal in compound **64**, but was still shifted downfield in comparison with the signal corresponding to the CH of the dimethylthienyl group, which was again in the same position as that of the CH of **21**. ^{13}C NMR analysis correlated well with predictions. Both spectra looked like combinations of the spectra of **50** and **46**, which would be expected.

Microanalysis data correlated well with calculated values for **94**. High-resolution MS analysis (EI^{+}) showed a peak at m/z = 433.0388, which correlated exactly with the

calculated mass for the molecular ion of **94**. More detailed characterisation data can be found in the experimental section.

The photochromic conversion of **94** to the closed form **95** is shown in **Scheme 4.10**.



94 **95**

Scheme 4.10: The reversible photochromic conversion of the acrylonitrile 94 to the closed form 95.

UV-Vis Spectroscopic analysis of a very light yellow methanol solution of **94** (7.96 x 10^{-5} mol dm^{-3}) showed an absorption at $\lambda = 364$ nm. This was expected due to the extension of conjugation of **94** in comparison with the previously discussed photochromic compounds resulting from the presence of the acrylonitrile moiety. Another peak was observed at $\lambda = 296$ nm. The solution was irradiated with UV light ($\lambda = 366$ nm) for 15 minutes, after which time it had developed a much brighter yellow colour (this can be seen in **Figure 4.8**). UV-Vis Spectroscopic analysis showed a decrease in the absorption at $\lambda = 360$ nm and the appearance of a new peak at $\lambda = 255$ nm and a small peak at $\lambda =$ 433 nm which were ascribed to the closed form of **94** (i.e. **95**). The yellow solution lost its colour when placed in direct sunlight. The colourless solution of **64** is shown in **Figure 4.8a** and the yellow solution of the photoconverted form **93** is shown in **Figure 4.8b**. The UV spectral change is shown in **Figure 4.9**.

In conclusion, the novel compound **94** has been synthesised *via* the successful Horner/Wadsworth/Emmons reaction of **64** with **55**, and has been shown to be photochromic.

The next stage of the synthesis involved the conversion of **94** to the final target molecule **45** by total reduction with $NaBH_4$ and $CoCl_2$ (previously used to convert **50** to **47**, as is reported in Chapter 3). It was also considered necessary to confirm that the

photochromic properties of **45** were identical to those of **21**, so that **45** would be shown to be a viable switchable RET acceptor for **1**.

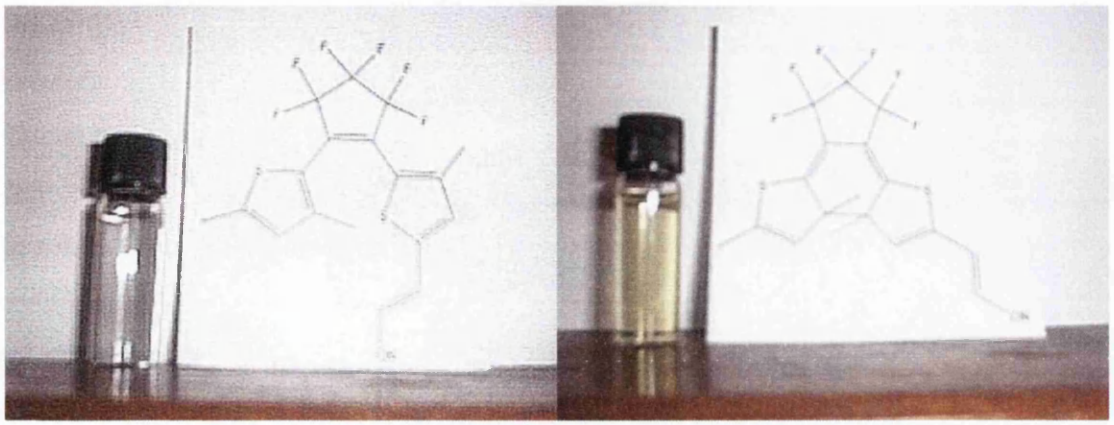


Figure 4.8a: The very light yellow solution of the A-form of the photochromic acrylonitrile (94)

Figure 4.8b: The yellow solution of the B-form of the photochromic acrylonitrile (95).

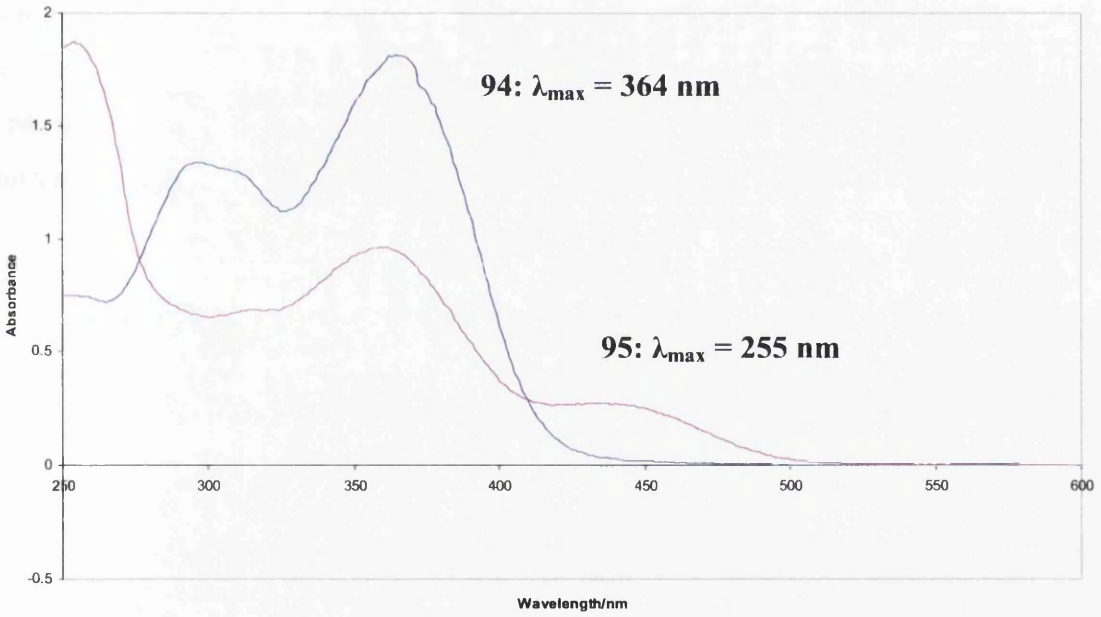
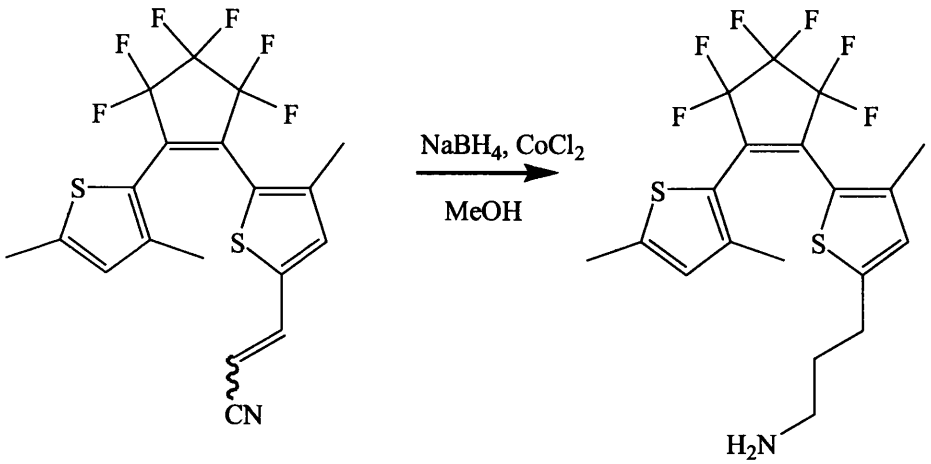


Figure 4.9: The UV-spectral change that accompanies the photochromic conversion of 94 to 95 (cf. Scheme 4.10). The very light yellow solution of open form 94 (cf. Figure 4.8a) exhibits an absorption at λ = 364 nm. Irradiation with UV light prompts the appearance of a much brighter yellow colour (cf. Figure 4.8b), which is accompanied by the reduction of the absorption at λ = 364 nm and the appearance of a new absorption at λ = 255 nm.

4.6. Synthesis of 1-([3-methyl-5-(3-amino-1-propyl)]-2-thienyl)-2-(3,5-dimethyl-2-thienyl)perfluorocyclopentene (45).

Compound **94** was dissolved in methanol with $NaBH_4$ and $CoCl_2$ and stirred overnight. 2M HCl was added to the mixture and the methanol was removed under reduced pressure, at which point a green solid precipitated out around the sides of the reaction vessel. It was thought that this solid was the hydrochloride salt of **45**, but it was not soluble in the aqueous phase as the hydrochloride salt of **47** had been. This was possibly due to the larger size of the molecule and also to the perfluorocyclopentene moiety, which was expected to be hydrophobic. The solid did dissolve in ethyl acetate, with which the aqueous phase was then extracted. The organic phase was treated with aqueous sodium hydroxide solution in the hope that this would produce the free amine **47**. The organic phase was washed with saturated aqueous sodium chloride solution and dried with anhydrous magnesium sulfate. The product solution was evaporated down and high-resolution MS analysis (EI^+) of the crude mixture showed a peak at $m/z = 440.0936$, which correlated exactly with the calculated value for the protonated form of **45**. ^1H NMR analysis of the product mixture also suggested that the desired product had been formed. The mixture was purified by column chromatography and **45** was isolated as a brown gum in 35 % yield. The reaction is shown in **Scheme 4.11**.



94 **45**

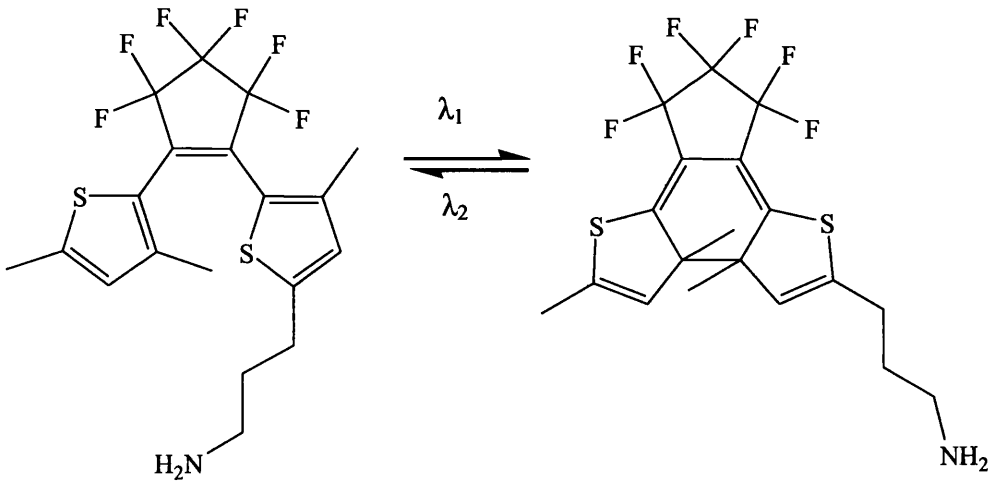
Scheme 4.11: Synthesis of the target molecule 45 by the reduction of 94 with $NaBH_4$ and $CoCl_2$.

^1H NMR analysis correlated well with predictions. The two thienyl CH signals were very close together near the chemical shift value of the CH of **21**, suggesting that the

signal of the CH proton of the aminopropylthienyl group was only shifted very slightly in comparison with the signal corresponding to the CH of the dimethylthienyl group, unlike the large downfield shifts observed for the analogous signals in the NMR spectra of the compounds **66**, **64** and **94**. The three expected CH_2 signals were present, as was the expected D_2O-exchanging NH_2 peak. ^{13}C NMR analysis showed the three expected new CH_2 signals and correlated well with predictions. Both spectra looked like combinations of the spectra of **46** and **47**, as was expected. High-resolution MS analysis showed a peak at $m/z = 440.0940$, which correlated well with the calculated value for the protonated form of **45** reported earlier.

While the structural elucidation based on NMR and MS was conclusive, product **45** was not produced in good yield. Furthermore, other signals that were apparent in the NMR spectra suggested that the sample was not pure even after purification by column chromatography, and further purification of the sample was not achieved even after further column chromatography. TLC analysis of the product mixture had revealed that the reaction had produced a mixture of several products and also included some of the starting material **94**. The other material would have been removed during extraction of the acidified aqueous phase if the hydrochloride salt of **45** had been soluble in the aqueous phase, but as it was not **45** had to be separated using column chromatography. The reason for the low yield of the product was not investigated due to time constraints, but it was thought prudent further to confirm the structure of the product by derivatisation. This was done successfully, as discussed in Section 4.7.

The photochromic conversion of **45** to the closed form **96** is shown in **Scheme 4.12**.



45 **96**

Scheme 4.12: The reversible photochromic conversion of 45 to the closed form 96.

UV-Vis Spectroscopic analysis of a colourless methanol solution of **64** (7.15×10^{-5} mol dm^{-3}, although this concentration is uncertain due to the uncertain purity of the sample of **45**) showed an absorption at $\lambda = 345$ nm, which correlated exactly with the measured value for **21** of $\lambda = 345$ nm in methanol. The solution was irradiated with UV light ($\lambda = 366$ nm) for 15 minutes, after which time it had developed a yellow colour (this can be seen in **Figure 4.10**). UV-Vis Spectroscopic analysis showed a decrease in the absorption at $\lambda = 345$ nm and the appearance of a new peak at $\lambda = 432$ nm which was ascribed to the closed form of **45** (i.e. **96**), correlating well with the measured value for the closed form of **21** (i.e. **22**) of $\lambda = 437$ nm. The yellow solution lost its colour when placed in direct sunlight. The colourless solution of **64** is shown in **Figure 4.10a** and the yellow solution of the photoconverted form **93** is shown in **Figure 4.10b**. The UV spectral change is shown in **Figure 4.11**.

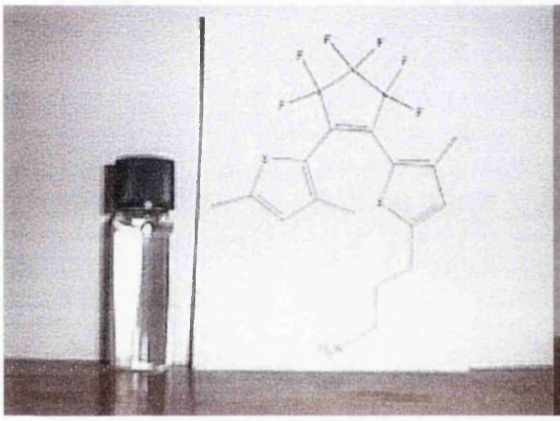


Figure 4.10a: The colourless solution of the A-form of the photochromic amine (45)

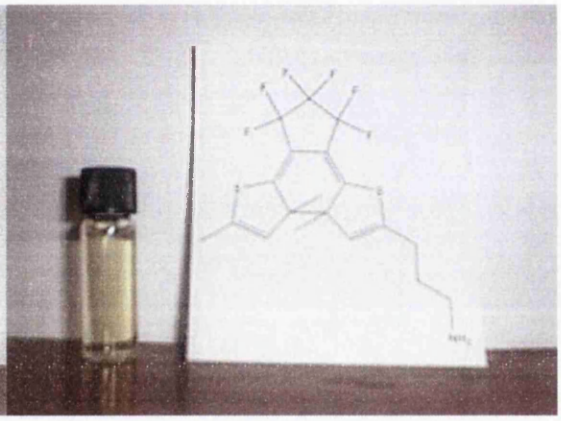


Figure 4.10b: The yellow solution of the B-form of the photochromic amine (96).

The UV spectral characteristics of **45** correlated exactly with those of **21**, indicating that the presence of the propylamino group had little or no effect on the photochromism of the molecule. The superimposed absorption spectra of **21** and **45** are shown in **Figure 4.12**, and the superimposed absorption spectra of **22** and **96** are shown in **Figure 4.13**.

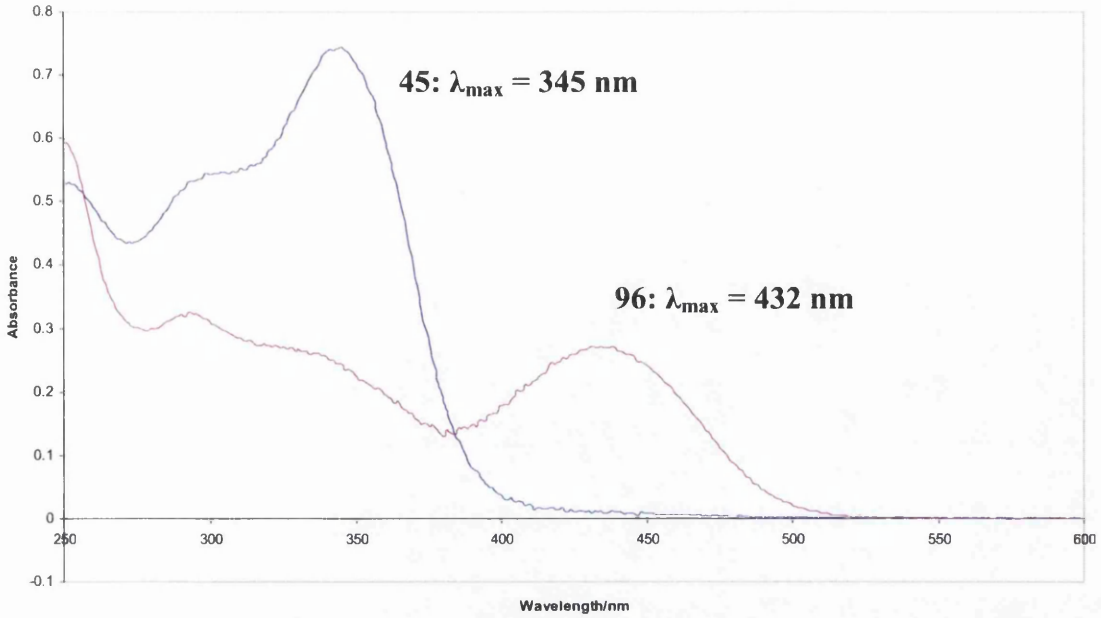


Figure 4.11: The UV-spectral change that accompanies the photochromic conversion of 45 to 96 (cf. Scheme 4.12). The colourless solution of open form 45 (cf. Figure 4.10a) exhibits an absorption at λ =345 nm. Irradiation with UV light prompts the appearance of yellow colour (cf. Figure 4.10b), which is accompanied by the reduction of the absorption at λ = 345 nm and the appearance of a new absorption at λ = 432 nm. This correlates well with the spectroscopic characteristics of the unmodified molecule 21 (cf. Figure 3.5).

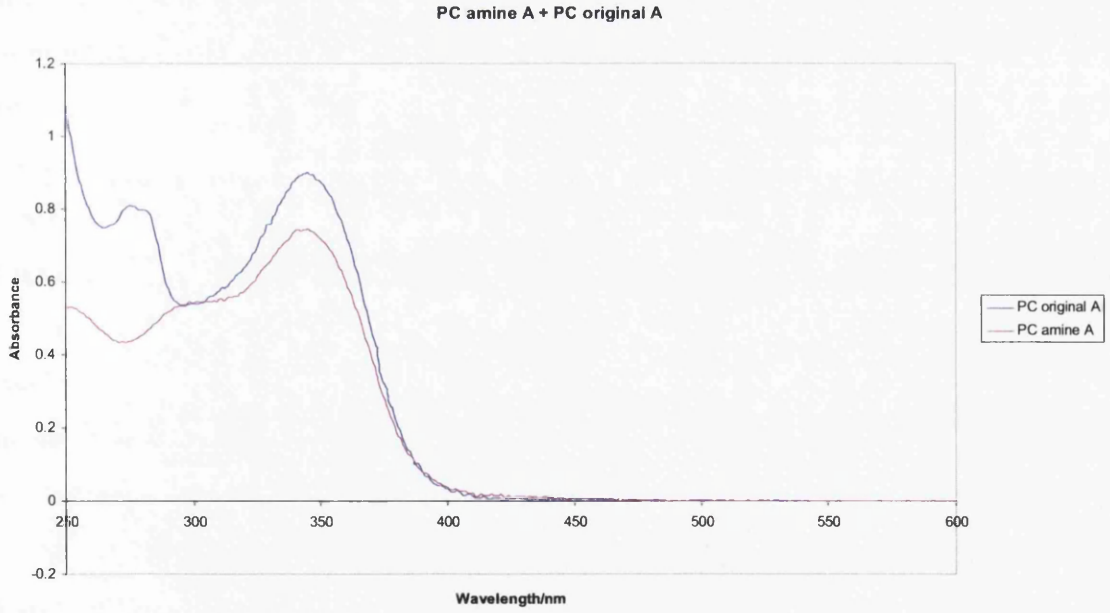


Figure 4.12: The superimposed absorption spectra of the original molecule 21 (represented by the blue line) and the modified linkable photochromic molecule 45 (represented by the purple line).

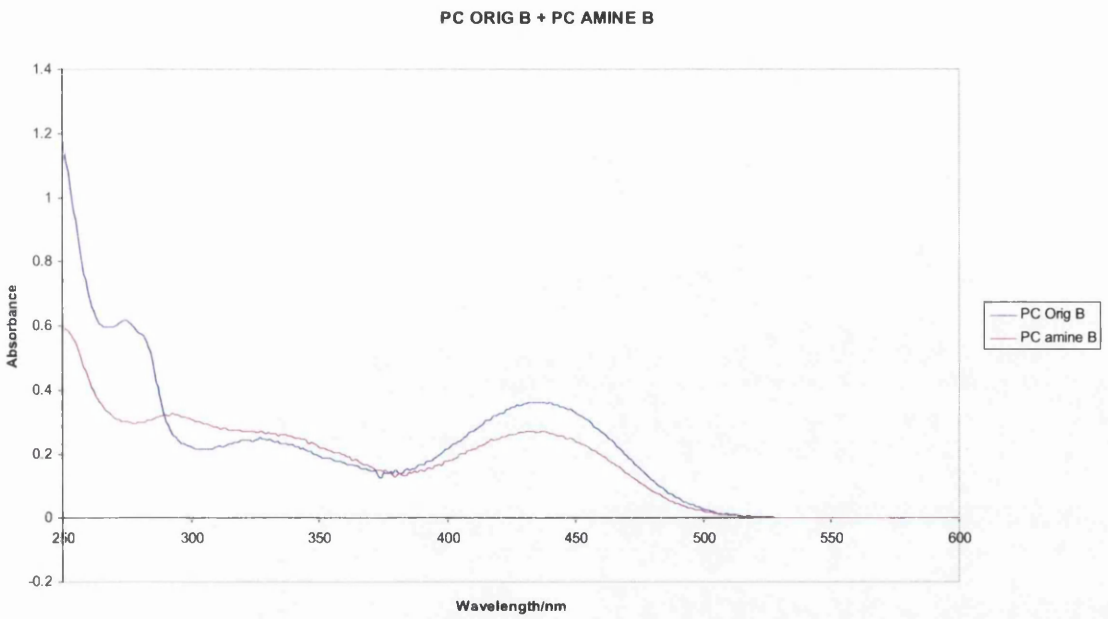


Figure 4.13: The superimposed absorption spectra of the closed form of the original photochromic molecule 21, (i.e. 22, represented by the blue line) and the closed form of the modified linkable photochromic molecule 45, (i.e. 96 represented by the purple line).

The spectral overlap integral of the closed form **96** and the fluorophore **1** was calculated using the same method that was employed in Section 3.2.3 for closed form of compound **21** (i.e. **22**). The spectral overlap integral ($J(\lambda)$) was found to be 1.13×10^{14} $dm^3mol^{-1}cm^{-1}nm^4$. This compared well with the value of 1.49×10^{14} $dm^3mol^{-1}cm^{-1}nm^4$ that was calculated for the donor-acceptor pair **1** and **22**. As the purity of the sample of **45** was not certain, the concentration of the solution of **45** used and the extinction coefficient values used to calculate $J(\lambda)$ are also uncertain. The spreadsheet used for the calculation of $J(\lambda)$ can be found in the experimental section.

This value of $J(\lambda)$ was used to calculate the value of R_0 for **1** and **96**, which was found to be 35.3 Å. This value was lower than the value of 36.9 Å calculated for **1** and **22**, but was still much larger than the planned donor-acceptor distance of 11.3 Å, and therefore **96** was confirmed to be a viable RET acceptor for the donor **1**. Furthermore, as the purity of **45** and therefore the concentration of the solution used was uncertain the value of R_0 can be considered to be a minimum value, and it is likely that the true value of R_0 is larger than that calculated in this instance. Regardless, it has been shown that the addition of the propylamino group to molecule **21** to form molecule **45** does not alter the photochromic characteristics significantly, and the linkable molecule **45** would be a viable switchable RET acceptor for the fluorophore **1**.

In conclusion, the novel compound **45** has been successfully synthesised via the reduction of **94** with $NaBH_4$ and $CoCl_2$. Compound **45** has been shown to have identical photochromic properties to those of the molecule **21**, indicating that the presence of the propylamino linker group does not modify the photochromic moiety to any significant degree. The UV data of the closed form **96** has been used to calculate the Förster distance for the donor-acceptor pair of **1** and **96**, which was found to be 35.3 Å (although the uncertainty regarding the purity of **45** lead to this being considered a minimum value). This shows that RET would occur if **1** and **96** were linked together with a donor-acceptor distance of 11.3 Å as planned.

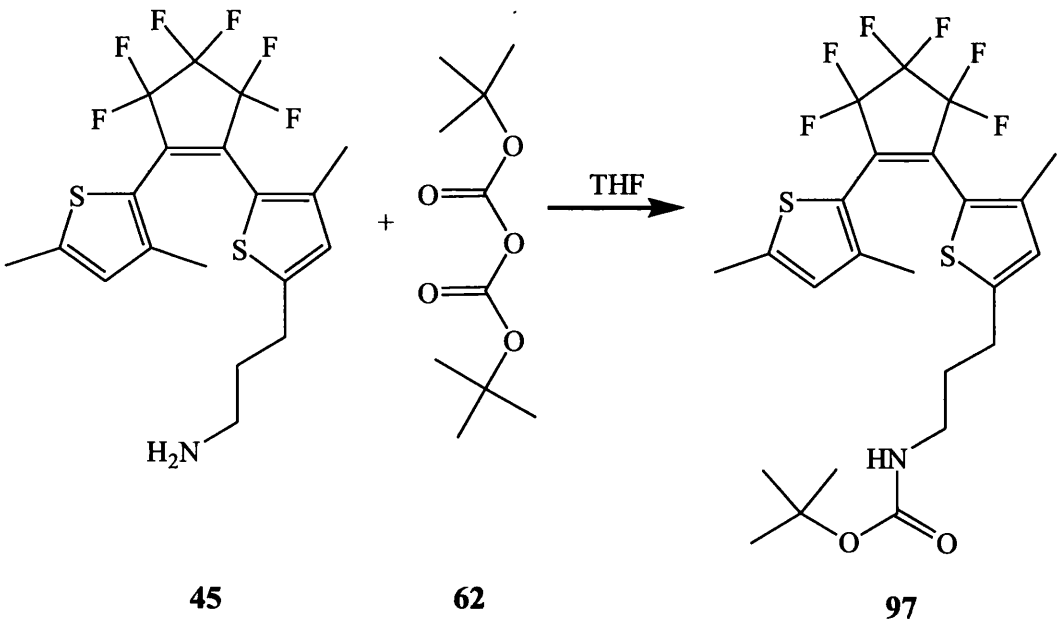
4.7. Derivatisation of 45.

As the synthesis of **45** reported in the previous section produced a product of uncertain purity and **45** was the ultimate target molecule of this entire project, it was considered necessary to synthesise a derivative of **45** to further confirm the structure. As amines can decompose in the presence of air it was also thought prudent to store **45** as a more stable derivative. As several protected derivatives of the amine **47** had been synthesised, as reported in Chapter 3, it was decided to use a similar strategy in this instance. As the trityl and TMT protection reactions were low-yielding they were not used. The Boc-protection reaction was simple and the Boc-protected derivative of **47** was isolated in 93 % yield, therefore this reaction was used for the synthesis of a derivative of **45**.

Compound **45** was dissolved in THF with Boc anhydride (**62**) and stirred overnight. Aqueous workup and purification by column chromatography afforded the product, (3-{5-[2-(3,5-dimethyl-2-thienyl)perfluorocyclopent-1-enyl]-4-methyl-2-thienyl}propyl)carbamic acid tert-butyl ester (**97**) as a dark yellow gum in 85 % yield. The reaction is shown in **Scheme 4.13**.

^{1}H NMR analysis correlated with expectations. The expected D_2O-exchanging NH signal was present at $\delta = 4.51$ ppm, and the signal corresponding to the CH_2 group positioned α-to the NH had been shifted down field and had lost fine structure in comparison with the analogous signal in the spectrum of **45**. This was similar to the effects noted in the previous Boc-protection reaction (Section 3.8.7). ^{13}C NMR analysis correlated well with predictions. Both spectra looked like combinations of the spectra of **46** and the previously synthesised Boc-protected amine **63**, which was expected. The

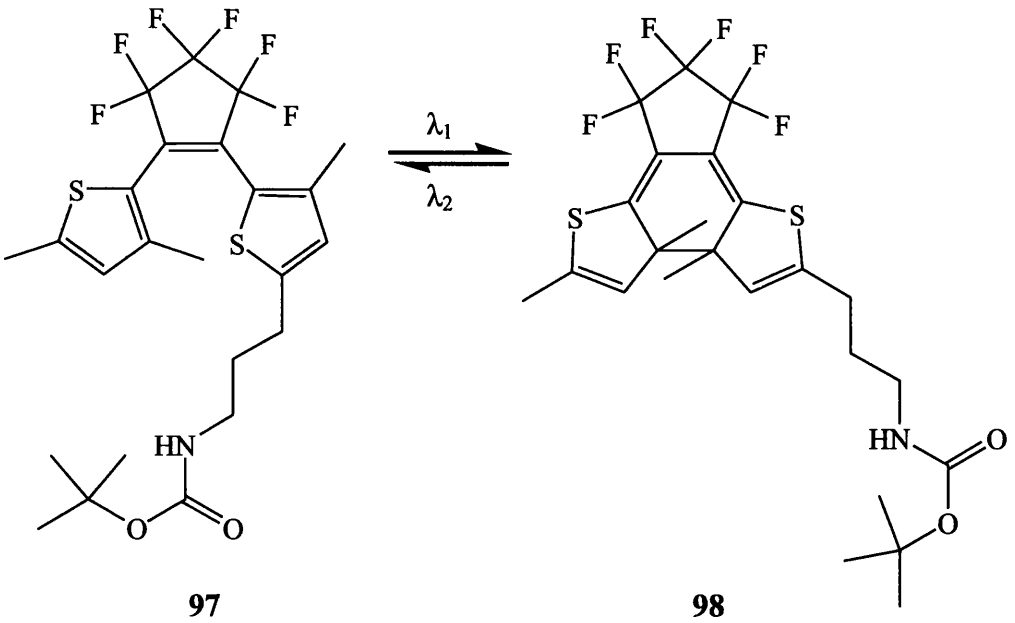
expected carbonyl signal was present in the IR spectrum. High-resolution MS analysis (ES^+) showed a peak at m/z = 562.1272, which correlated well with the calculated value for the $[M+Na]^+$ ion of **97**, 562.1280.



45 **62** **97**

Scheme 4.13: Protection of 45 as the Boc derivative 97 by reaction with 62 in THF.

The photochromic conversion of **97** to the closed form **98** is shown in **Scheme 4.14**.



97 **98**

Scheme 4.14: The reversible photochromic conversion of 97 to the closed form 98.

UV-Vis Spectroscopic analysis of a colourless methanol solution of **97** (4.99×10^{-5} mol dm^{-3}) showed an absorption at $\lambda = 344$ nm, which correlated well with the measured value for **21** of $\lambda = 345$ nm in methanol and the measured value for **45** of 345 nm. The solution was irradiated with UV light ($\lambda = 366$ nm) for 15 minutes, after which time it had developed a yellow colour (this can be seen in **Figure 4.14**). UV-Vis Spectroscopic analysis showed a decrease in the absorption at $\lambda = 344$ nm and the appearance of a new peak at $\lambda = 435$ nm which was ascribed to the closed form of **97** (i.e. **98**), correlating well with the measured value for the closed form of **21** (i.e. **22**) of $\lambda = 437$ nm and the value for the closed form of **45** (i.e. **96**), 432 nm. The yellow solution lost its colour when placed in direct sunlight. The colourless solution of **97** is shown in **Figure 4.14a** and the yellow solution of the photoconverted form **98** is shown in **Figure 4.14b**. The UV spectral change is shown in **Figure 4.15**.

The product of the Boc-protection can be seen to have identical photochromic properties both to the original photochromic compound **21** and to the modified linkable photochromic amine **45**.

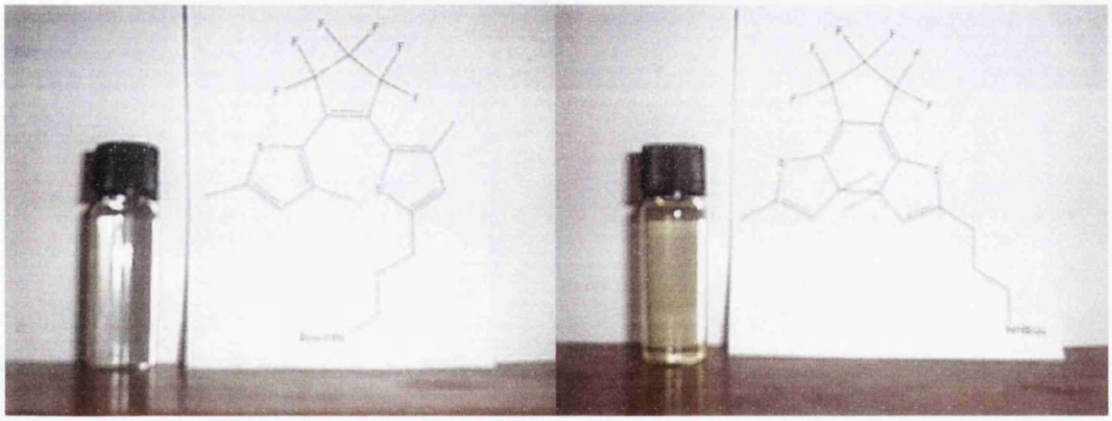


Figure 4.14a: The colourless solution of the A-form of the Boc-protected photochromic amine (97)

Figure 4.14b: The yellow solution of the B-form of the Boc-protected photochromic amine (98).

The successful synthesis and characterisation of **97**, the Boc protected derivative of **45**, provided more evidence that **45** had been successfully synthesised. In order to provide further evidence that the project had been a success, two simple deprotection reactions were carried out with the aim of identifying the molecular ions of the products by high-resolution MS analysis.

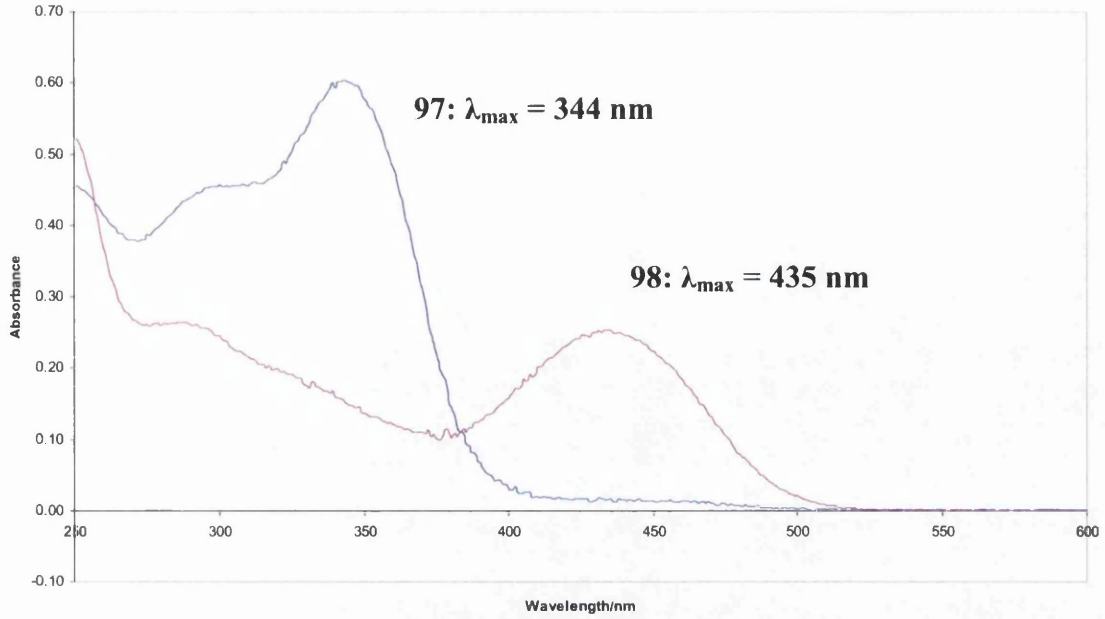


Figure 4.15: The UV-spectral change that accompanies the photochromic conversion of 97 to 98 (cf. Scheme 4.14). The colourless solution of open form 97 (cf. Figure 4.14a) exhibits an absorption at λ =344 nm. Irradiation with UV light prompts the appearance of yellow colour (cf. Figure 4.14b), which is accompanied by the reduction of the absorption at λ = 344 nm and the appearance of a new absorption at λ = 435 nm. This correlates well with the spectroscopic characteristics of the unmodified molecule 21 (cf. Figure 3.5) and the photochromic amine 45 (cf. Figure 4.11).

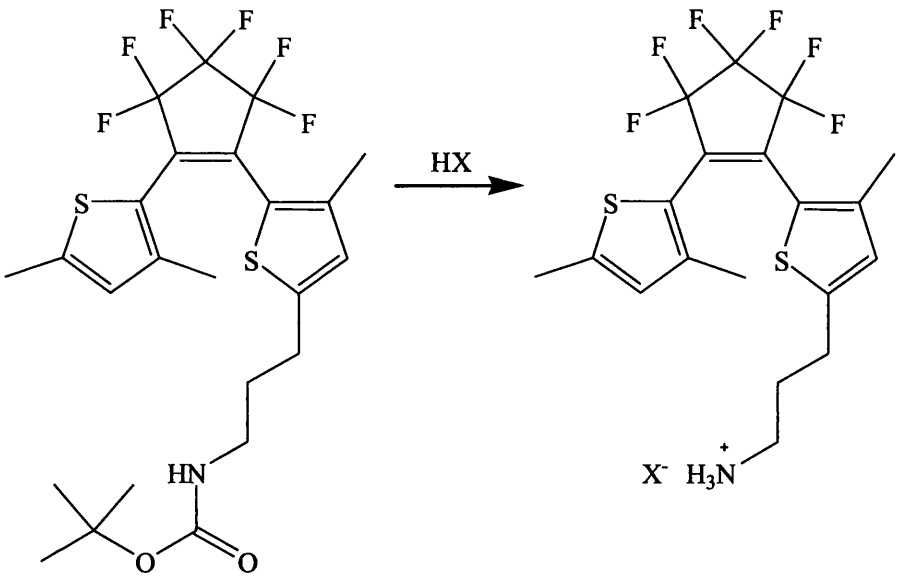
The first deprotection reaction, shown in **Scheme 4.15** (X = Cl), involved refluxing a small amount of **97** with concentrated HCl in methanol in the hope of forming the hydrochloride salt of **45**, 1-([3-methyl-5-(3-amonio-1-propyl)]-2-thienyl)-2-(3,5-dimethyl-2-thienyl)perfluorocyclopentene hydrochloride (**99**, X = Cl).

The reaction proceeded successfully, and after removal of the solvents under reduced pressure, high-resolution MS analysis (ES^+) showed a peak at *m/z* = 440.0934, which correlated well with the calculated value for the cation of **99**, 440.0936. The product was not rigorously characterised due to time constraints, but the presence of the correct cation was considered sufficient evidence that the reaction was successful.

The second deprotection reaction, shown in **Scheme 4.15** (X = CF_3COO), involved stirring a small amount of **97** with trifluoroacetic acid in the hope of forming the trifluoroacetate salt of **45**, 1-([3-methyl-5-(3-ammonio-1-propyl)]-2-thienyl)-2-(3,5-dimethyl-2-thienyl) perfluorocyclopentene trifluoroacetate (**99**, X = CF_3COO).

The reaction proceeded successfully, and after removal of the solvents under reduced pressure, high-resolution MS analysis (ES^+) showed a peak at *m/z* = 440.0940, which

correlated well with the calculated value for the cation of **99**, 440.0936. The product was again not rigorously characterised due to time constraints, but the presence of the correct cation was considered sufficient evidence that the reaction was successful.



97 **99**

Scheme 4.15: Deprotection of 97 with acid to give a salt of 45. (99, X = Cl or CF_3COO).

In conclusion, the novel compound **97**, which is the Boc-protected derivative of the ultimate target molecule **45**, has been successfully synthesised via the reaction of **45** with **62** in THF. Compound **97** was obtained in a pure form and the characterisation data obtained for **97** provides more evidence for the structure of **45**. The photochromic characteristics of **97** are almost identical to those of **45** and **21**, suggesting the presence of the Boc-aminopropyl group has no effect on the photochromic moiety. Compound **97** was deprotected using HCl and trifluoroacetic acid, and MS analysis of the products of both reactions showed the presence of the protonated cation of **45**, as expected.

4.8. Conclusion to Chapter 4.

The target molecule 1-([3-methyl-5-(3-amino-1-propyl)]-2-thienyl)-2-(3,5-dimethyl-2-thienyl)perfluorocyclopentene (**45**) has been successfully synthesised *via* the known compound **51** and the novel compounds **65**, **66**, **64** and **94**. The overall yield of the synthesis is 12.6 % (based on the starting material 3-methylthiophene (**38**)),

but this is largely due to the relatively low isolated yield of **66** and the low yield of the final reduction reaction of **94** to give **45**. All other reactions are high-yielding.

Compound **45** has been shown to be photochromic, and furthermore to exhibit almost identical photochromic characteristics to the unmodified photochromic molecule **21**. The Förster distance of a donor-acceptor pair consisting of the fluorophore *N*-methylacridone (**1**) and the closed form of **45** (**96**) has been found to be 35.3 Å, which indicates that switchable RET will occur if **1** and **45** are linked together with a donor-acceptor distance of 11.3 Å as planned.

Compound **45** has been protected as the Boc-derivative **97** in order to further confirm the structure of **45** and as a means of storing **45**. The information obtained for the structure of **97** further confirmed that **45** has been successfully synthesised, as did the information gained from the deprotection reactions of **97**.

Compounds **66**, **64**, **94** and **97** have all been shown also to be photochromic.

The low-yielding final reduction of **94** to form **45** was not rigorously investigated due to time constraints, but the higher yield obtained for the reduction of **50** to form **47**, as reported in Chapter 3, suggests that the yield of the reaction should be higher. Further work could involve attempting to improve the yield of the final reaction. It would perhaps be prudent to perform a conjugate reduction first and then reduce the nitrile group, as suggested in Chapter 1, Section 1.11.1, as conjugate reductions are reported to be high-yielding. The presence of the acrylonitrile group altered the photochromic characteristics of the molecule considerably, and it would be interesting to see what effect removing the conjugation while retaining the nitrile group would have.

4.9. Experimental.

4.9.1. General Experimental

See Chapter 2 section 2.6.1.

*4.9.2. GC Conditions for **65**.*

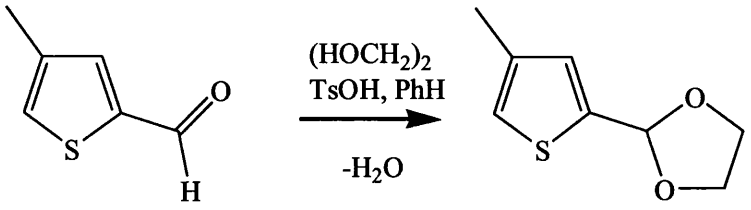
Instrument	Hewlett Packard HP5890 Series II
	Gas Chromatograph
Column	Zorbax ZB-5 5% Phenyl 95% Dimethylpolysiloxane
	30m length 0.32mm i.d.
Injection Mode	Splitless. Purge on at 0.7 minutes.
Injection Volume	0.5μL
Injector Temperature	300 °C
Detector Temperature	300 °C
Temperature Programme	60 °C for 0 minutes
	Ramp A 3 °C/min to 95 °C. Hold for 0 minutes
	Ramp B 5 °C/min to 200 °C. Hold for 5 minutes.
	Ramp C 5 °C/min to 340 °C. Hold for 15 minutes.
Detector Attenuation	0
Detector Range	4
Integrator Attenuation	10
Integrator Chart Speed	0.2 cm/min
Integrator Area Rejection	50 1/8 μV-sec
Integrator Threshold	11
Integrator Peak Width	0.04 min

4.9.3. GC Conditions for photochromic compounds.

GC conditions are identical to those given in Section 4.9.2., with the exception of the temperature programme used

Temperature Programme	60 °C for 0 minutes
	Ramp A 12 °C/min to 200 °C. Hold for 0 minutes
	Ramp B 5 °C/min to 340 °C. Hold for 40 minutes.

4.9.4. Synthesis of 2-(4-methyl-2-thienyl)-[1,3]dioxolane (65).

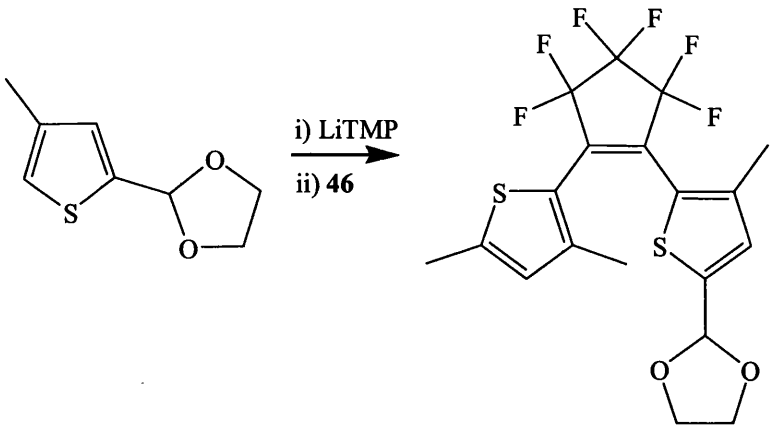


51 **65**

Scheme 4.16: Protection of aldehyde 51 by reaction with ethylene glycol to give the cyclic acetal 65.

4-Methyl-2-thiophenecarboxaldehyde (**51**, 5.6 g, 44 mmol), ethylene glycol (5.8 g, 94 mmol) and *para*-toluenesulfonic acid monohydrate (0.84 g, 4.4 mmol) were dissolved in benzene (100 mL) in a 250 mL round-bottom flask fitted with a foil-lagged Dean & Stark trap and a condenser. The mixture was refluxed at 135 °C overnight by which point water had ceased to accumulate in the Dean & Stark trap. The mixture was allowed to cool to room temperature and saturated aqueous sodium hydrogen carbonate solution (100 mL) was added. The mixture was extracted with ethyl acetate (6 x 100 mL). The dark brown organic phase was washed with saturated aqueous sodium chloride solution and dried with anhydrous magnesium sulfate, filtered and then treated with activated charcoal (approx. 2 g, stirred at room temp. for 20 min.) and filtered again to give a clear yellow solution. The solution was evaporated and distilled under reduced pressure to give the product **65** as a clear, colourless oil (bp 264 °C) in 85% yield (6.35 g, 37.3 mmol) and 97.6% purity (GC). ν_{max} (film) /cm^{-1} 1066 (C-O-C). δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.25 (3H, s, thienyl C*H*$_3$), 4.05, 4.15 (2 x 2H, 2m, acetal C*H*$_2$), 6.08 (1H, s, acetal C*H*), 6.91 (1H, s, thienyl 3-*H*), 7.00 (1H, s, thienyl 5-*H*). δ_C (100 MHz; $CDCl_3$ Me_4Si) 16.1 (thienyl *C*H$_3$), 65.6 (acetal (*C*H$_2$)$_2$), 100.0 (acetal *C*H), 125.1 (thienyl 5-*C*H), 128.6 (thienyl 3-*C*H), 139.6 (thienyl 4-*C*), 144.0 (thienyl 2-*C*). *m/z* (ES$^+$) = 171.0475 ([M+H]$^+$ $C_8H_{11}O_2S$ requires 171.0474). *m/z* (EI$^+$) 170 ([M]$^+$ 54 %), 155 ([M-CH$_3$]$^+$ 4 %), 125 (66 %), 111 (41 %), 98 (100 %), 73 (26 %), 45 (38 %). *m/z* (CI$^+$(NH$_3$)) 171 ([M+H]$^+$, 100 %), 144 (4 %), 52 (12 %).

*4.9.5. Synthesis of 2-{5-[2-(3,5-dimethyl-2-thienyl)perfluorocyclopent-1-enyl]-4-methyl-2-thienyl}-[1,3]dioxolane (**66**).*



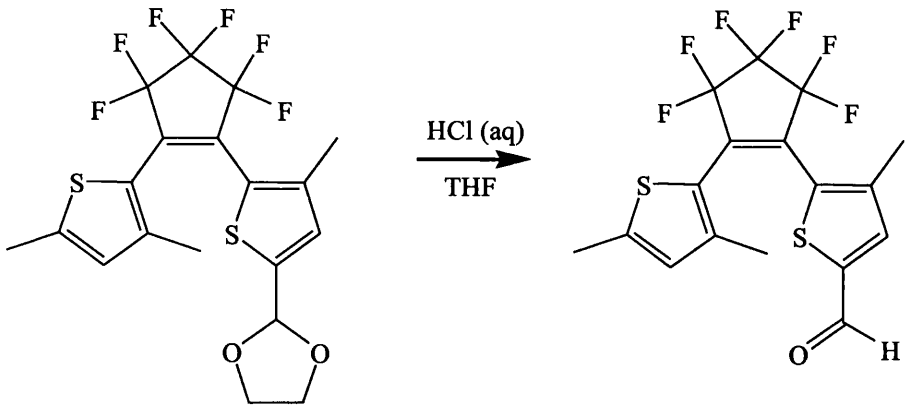
65 **66**

Scheme 4.17: lithiation of cyclic acetal 65 and reaction with 46 to give the photochromic acetal 66.

2,2,6,6-Tetramethylpiperidine (2.03 g, 14.3 mmol) was dissolved in dry, distilled THF (50 mL) in a 250 mL round-bottom flask under an argon atmosphere and cooled in a dry ice/acetone bath. *tert*-Butyllithium (8.5 mL of a 1.7 mol dm^{-3} solution in pentane, 14.5 mmol) was added dropwise *via* syringe and the resulting bright yellow solution was stirred for 1 hour. 2-(4-Methyl-2-thienyl)-[1,3]dioxolane (**65**, 2.30 g, 13.5 mmol) was added *via* syringe and the resulting dark red/brown solution was stirred for 1 hour. 1-(3,5-Dimethyl-2-thienyl)perfluorocyclopentene (**46**, 4.0 g, 13.1 mmol) was added *via* syringe over 5 min and the resulting dark red/brown solution was stirred for 48 hours at room temp. Saturated aqueous ammonium chloride solution (75 mL) was added to quench the reaction and the mixture was extracted with ethyl acetate (6 x 75 mL). The organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (100 mL), and saturated aqueous sodium chloride solution (10 mL) and dried with anhydrous magnesium sulfate. GC analysis showed the product in 67% purity with significant amounts of both starting materials present. The solution was evaporated and purification by silica gel chromatography (hexane to remove the electrophile **46** then gradient eluted up to 20% diethyl ether/ hexane) and subsequent recrystallisation (Et_2O/hexane) gave the product **66** as bright yellow crystals (mp 109.9-111.3 °C) in 58 % yield (3.56 g, 7.84 mmol) and 98.6 % purity (GC). Anal. Found: C 50.27, H 3.50 %. Calc. for $C_{19}H_{16}F_6O_2S_2$: C 50.22, H 3.55 %. ν_{max} (film) /cm^{-1} 1073 (C-O-C). λ_{max} (MeOH)/nm 339 (ε/$dm^3mol^{-1}cm^{-1}$ 1.16 x 10^4). After irradiation with light at 366 nm for 15 minutes:

435 (5.00 x 10^3). δ_H (400 MHz; acetone-d^6; Me_4Si) 1.71, (3H, s, CH_3), 1.75 (3H, s, CH_3), 2.44 (3H, s, dimethylthienyl 5-CH_3), 4.04, 4.09 (2 x 2H, 2m, acetal CH_2), 6.08 (1H, s, acetal *CH*), 6.71 (1H, s, dimethylthienyl *CH*), 7.08 (1H, s, acetal-substituted thienyl *CH*). δ_C (100 MHz; acetone-d^6; Me_4Si, 5000 scans) 15.6, 15.8, 15.9 (3 x CH_3), 66.4 (acetal CH_2), 100.6 (acetal *CH*), 112.2 (tm, $^1J_{C-F}$ = 273 Hz, perfluorocyclopentenyl 4-*C*), 117.1, 117.2 (tm, $^1J_{C-F}$ = 253 Hz, tm, $^1J_{C-F}$ = 260 Hz perfluorocyclopentenyl 3-*C*, 5-*C*.) 121.3 (dimethylthienyl 2-*C*) 124.3 (acetal-substituted thienyl 2-*C*), 130.9, 131.1 (acetal-substituted thienyl 4-*C*H, dimethylthienyl 4-*C*H), 134.2 (m, perfluorocyclopentenyl 2-*C*), 136.5 (m, perfluorocyclopentenyl 1-*C*), 142.4, 143.3 (dimethylthienyl 3-*C*, acetal-substituted thienyl 3-*C*), 146.6, 148.1 (dimethylthienyl 5-*C*, acetal-substituted thienyl 5-*C*). δ_F (376 MHz, acetone-d^6) -131.2 (4-*F*), -109.3, -109.1 (3-*F*, 5-*F*). *m/z* (ES^+) = 455.0570 ($[M+H]^+$ $C_{19}H_{17}F_6O_2S_2$ requires 455.0569). *m/z* (EI^+) = 454 ($[M]^+$ 50 %), 439 ($[M-CH_3]^+$ 4 %), 409 (8 %), 382 (38 %), 73 (63 %), 45 (100 %). *m/z* ($CI^+(NH_3)$) = 455 ($[M+H]^+$, 100 %), 437 (6 %), 52 (36 %).

4.9.6. *Synthesis of 5-[2-(3,5-dimethyl-2-thienyl)perfluorocyclopent-1-enyl]-4-methyl-2-thiophenecarboxaldehyde(**64**).*



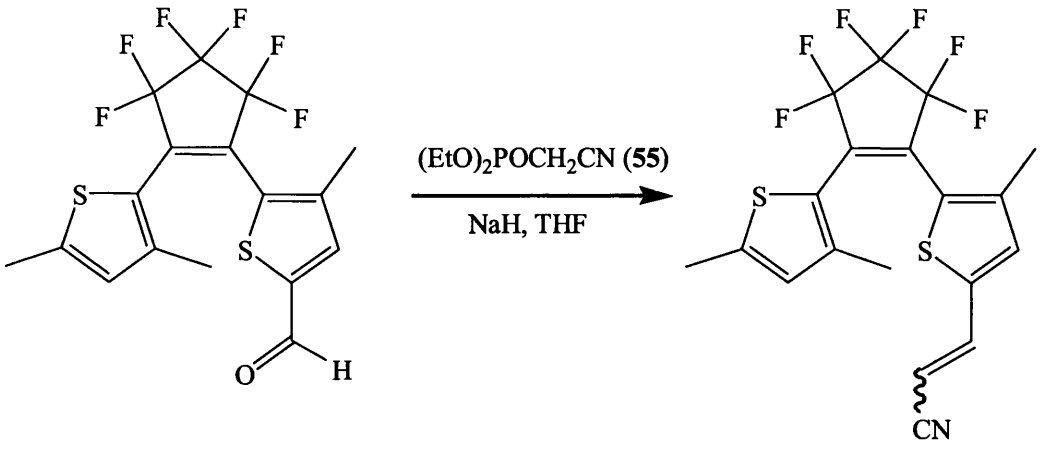
66 **64**

Scheme 4.18: The deprotection reaction of the acetal 66 with HCl to form the aldehyde 64.

2-{5-[2-(3,5-Dimethyl-2-thienyl)perfluorocyclopent-1-enyl]-4-methyl-2-thienyl}-[1,3]dioxolane (**66**, 1.17 g, 2.57 mmol) was dissolved in THF (20 mL). To the resultant bright yellow solution aqueous HCl (10 %, 25 mL) was added, at which point the reaction mixture warmed up. The mixture was stirred overnight. The reaction was neutralised with powdered sodium hydrogen carbonate and the mixture was extracted with ethyl acetate (4

x 75 mL). The organic phase was washed with saturated aqueous sodium chloride solution (100 mL) and dried with anhydrous magnesium sulfate. GC analysis showed the product **64** in 98 % purity. The dry solution was filtered, evaporated and upon recrystallisation (Et_2O/hexane) the product was obtained as yellow crystals (mp 79.5 - 80.7 °C) in 92 % yield (0.970 g, 2.36 mmol) and 99.5 % purity (GC). Anal. Found: C 49.81, H 2.92 %. Calc. for $C_{17}H_{12}F_6OS_2$: C 49.75, H 2.95 %. ν_{max} (film) /cm^{-1} 1670 (C=O). λ_{max} (MeOH)/nm 349 (ε/$dm^3mol^{-1}cm^{-1}$ 1.14 x 10^4). After irradiation with light at 366 nm for 15 minutes: 439 (3.72 x 10^3). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.68 (3H, s, dimethylthienyl 3-C*H*$_3$), 1.78 (3H, s, formyl-substituted thienyl 3-C*H*$_3$), 2.50 (3H, s, dimethylthienyl 5-C*H*$_3$),), 6.48 (1H, s, dimethylthienyl C*H*), 7.44 (1H, s, formyl-substituted thienyl C*H*), 9.79 (1H, s, C*H*O). δ_C (100 MHz; $CDCl_3$; Me_4Si, 5000 scans) 15.4, 15.7, 15.9 (3 x *C*H$_3$), 111.1 (tm, $^1J_{C\text{-}F}$ = 263 Hz, perfluorocyclopentenyl 4-*C*), 115.8, 115.9 (tm, $^1J_{C\text{-}F}$ = 256 Hz, tm, $^1J_{C\text{-}F}$ = 260 Hz perfluorocyclopentenyl 3-*C*, 5-*C*.), 120.5 (dimethylthienyl 2-*C*), 130.2 (dimethylthienyl 4-*C*H), 131.7 (m, perfluorocyclopentenyl 2-*C*), 132.9 (formyl-substituted thienyl 2-*C*), 138.2, (perfluorocyclopentenyl 1-*C*), 138.5 (formyl-substituted thienyl *C*H), 142.0, 142.7 (formyl-substituted thienyl 3-*C*, dimethylthienyl 3-*C*), 145.49, 146.10 (dimethylthienyl 5-*C*, formyl-substituted thienyl 5-*C*), 182.9 (*C*HO). δ_F (376 MHz, $CDCl_3$) -131.2 (4-*F*), -109.6, -108.8 (3-*F*, 5-*F*). *m/z* (ES^+) = 411.0307 ($[M+H]^+$ $C_{17}H_{13}F_6OS_2$ requires 411.0307). *m/z* (EI^+) = 410 ($[M]^+$ 36 %), 395 ($[M\text{-}CH_3]^+$ 7%), 111 (22 %), 69 (64 %), 59 (100 %), 45 (78 %). *m/z* ($CI^+(NH_3)$) = 428 ($[M+NH_4]^+$ 42 %), 410 ($[M]^+$ 53 %), 377 (29 %), 363 (32 %), 113 (90 %).

4.9.7. Synthesis of 3-{5-[2-(3,5-dimethyl-2-thienyl)perfluorocyclopent-1-enyl]-4-methyl-2-thienyl}acrylonitrile (94).



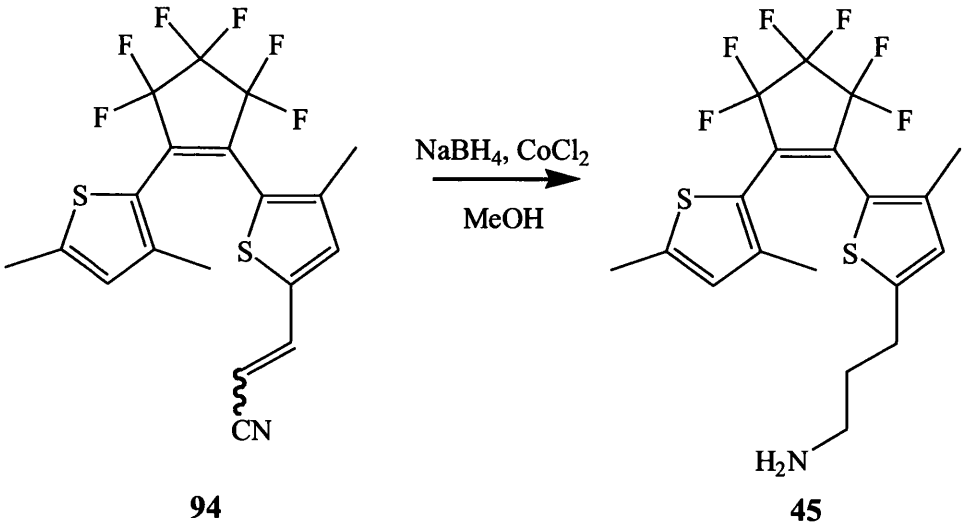
64 **94**

Scheme 4.19: The Horner/Wadsworth/Emmons reaction of 64 with 55 to form 94.

Sodium hydride (0.12 g of a 60 % dispersion in mineral oil, 3.00 mmol) was washed 3 times successively with dry, distilled hexane and then suspended in dry, distilled THF (60 mL). To the resulting grey suspension was added diethylcyanomethylphosphonate (**55**, 0.486 g, 2.74 mmol) *via* syringe. The resulting light yellow solution was stirred for 1 hour. 5-[2-(3,5-Dimethyl-2-thienyl)perfluorocyclopent-1-enyl]-4-methyl-2-thiophenecarboxaldehyde (**64**, 0.945 g, 2.30 mmol) was dissolved in dry, distilled THF (10 mL) and added to the solution *via* syringe over 10 min. The resulting dark green solution was stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride solution (30 mL) and extracted with ethyl acetate (5 x 75 mL). The organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (100 mL) and saturated aqueous sodium chloride solution (10 mL) and dried over anhydrous magnesium sulfate. The resulting brown solution was treated with activated charcoal (approx. 2 g, stirred at room temp. for 20 min.) to give a bright yellow solution. GC analysis showed two product peaks in a ratio of 5.5:1 which were thought to be the *E*- and *Z*-isomers of the product respectively. The solution was evaporated and after purification by silica gel chromatography (50% Et_2O/hexane) and subsequent recrystallisation (Et_2O/hexane) the product **94**-was obtained as yellow crystals (mp 140.9-149.2 °C – the large range was thought to be due to the presence of both *E*- and *Z*-isomers)

in 89 % yield (0.89 g, 2.05 mmol) and 98.2 % purity (GC – sum of areas of both peaks). *E*:*Z* ratio = 5.5:1 (GC/NMR). Anal. Found: C 52.52, H 3.03, N 3.14 %. Calc. for $C_{19}H_{14}F_6S_2N$: C 52.50, H 3.25, N 3.22 %. ν_{max} (film) /cm^{-1} 2215.64 (CN). λ_{max} (MeOH)/nm 364 (ε/$dm^3mol^{-1}cm^{-1}$ 2.28 x 10^4). After irradiation with light at 366 nm for 15 minutes: 255 (2.35 x 10^4). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.66, 1.69 (3H, s, dimethylthienyl 3-C*H*$_3$, 3H, s, cyanoethenylthienyl 3-C*H*$_3$), 2.39 (3H, s, dimethylthienyl 5-C*H*$_3$), 5.25 (0.15H, d, *J* = 12 Hz, *Z*-isomer CH=C*H*CN), 5.60 (0.85H, d, *J* = 16 Hz, *E*-isomer CH=C*H*CN), 6.45 (1H, s, dimethylthienyl 4-*H*), 76.93 (1H, s, cyanoethenylthienyl 4-*H*), 7.02 (0.15H, d, *J* = 12 Hz, *Z*-isomer C*H*=CHCN), 7.29 (0.85H, d, *J* = 16 Hz, *E*-isomer C*H*=CHCN) δ_C (100 MHz; $CDCl_3$; Me_4Si, 5000 scans). 15.4, 15.8, 15.9 (3 x *C*H$_3$), 94.3 (*Z*-isomer CH*C*HCN), 96.8 (*E*-isomer CH*C*HCN), 111.1 (tm, $^1J_{C\text{-}F}$ = 272 Hz, perfluorocyclopentenyl 4-*C*), 115.8, 116.0 (tm, $^1J_{C\text{-}F}$ = 233 Hz, tm, $^1J_{C\text{-}F}$ = 242 Hz perfluorocyclopentenyl 3-*C*, 5-*C*.), 117.6 (*Z*-isomer *C*N), 118.0 (*E*-isomer *C*N), 120.8 (dimethylthienyl 2-*C*), 127.3 (cyanoethenylthienyl 2-*C*), 130.1 (dimethylthienyl 4-*C*H), 131.7 (m, perfluorocyclopentenyl 2-*C*), 134.3 (cyanoethenylthienyl 4-*C*H), 137.2 (m, perfluorocyclopentenyl 1-*C*), 139.8 (*Z*-isomer *C*HCHCN), 141.0 (cyanoethenylthienyl 5-C), 142.0 (*E*-isomer *C*HCHCN), 142.3, 142.5 (cyanoethenylthienyl 3-*C*, dimethylthienyl 3-*C*), 145.83 (dimethylthienyl 5-*C*). δ_F (376 MHz, $CDCl_3$) -131.2 (4-*F*), -109.4, -108.7 (3-*F*, 5-*F*). *m/z* (EI^+) = 433.0388 ($[M]^+$ $C_{19}H_{14}F_6S_2N$ requires 433.0388). *m/z* (EI^+) = 433 ($[M]^+$ 100%), 418 ($[M\text{-}CH_3]^+$ 31 %), 398 (16%), 380 (25%), 360 (20%), 217 (15 %), 111 (17 %). *m/z* ($CI^+(NH_3)$) 453 (62 %), 433 ($[M]^+$, 12 %), 113 (68 %).

4.9.8 Synthesis of 1-([3-methyl-5-(3-amino-1-propyl)]-2-thienyl)-2-(3,5-dimethyl-2-thienyl)perfluorocyclopentene (45).



94 **45**

Scheme 4.20: Synthesis of the target molecule 45 by the reduction of 94 with $NaBH_4$ and $CoCl_2$.

3-{5-[2-(3,5-Dimethyl-2-thienyl)perfluorocyclopent-1-enyl]-4-methyl-2-thienyl}acrylonitrile (**94**, 0.501 g, 1.16 mmol) was dissolved in methanol (50 mL) in a 100 mL round-bottomed flask and anhydrous cobalt (II) chloride (0.33 g, 2.40 mmol) was added. The cloudy pink suspension was cooled in ice/water. Sodium borohydride (0.448 g, 11.8 mmol) was added gradually in small portions. The mixture gave off gas and a black precipitate was produced. The mixture was stirred overnight. Hydrochloric acid (4M, 40 mL) was added, at which point the precipitate dissolved and a cloudy pink solution resulted. The methanol was removed under reduced pressure, at which point the hydrochloride salt of the product precipitated out around the sides of the vessel. The resulting mixture was extracted with ethyl acetate (4 x 75 mL) in which the solid dissolved. The organic phase was washed with 3M aqueous sodium hydroxide solution (2 x 50 mL), saturated aqueous sodium hydrogen carbonate solution (50 mL) and saturated aqueous sodium chloride solution (50 mL). The resulting brown solution was dried with anhydrous magnesium sulfate and treated with activated charcoal (approx. 2 g, stirred at room temp. for 20 min.). The resulting yellow solution was evaporated and the residue was somewhat purified by column chromatography (alumina, 80 % EtOAc/hexane up to 30 % MeOH/EtOAc). The product, **45** was isolated as a brown gum in 35 % yield (0.178 g, 0.40 mmol). λ_{max} (MeOH)/nm 345. After irradiation with light at 366 nm for 15

minutes: 432 nm; the purity of the sample was uncertain so exact extinction coefficient values could not be calculated reliably. δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.20 (2H, s, D_2O Ex. NH_2), 1.61, 1.63 (3H, s, dimethylthienyl 3-CH_3, 3H, s, aminopropylthienyl 3-CH_3), 1.83 (2H, quintet, J = 8 Hz, $CH_2CH_2NH_2$), 2.38 (3H, s, dimethylthienyl 5-CH_3), 2.65, 2.76 (2H, t, J = 8 Hz, $CH_2CH_2CH_2NH_2$, 2H, t, J = 8 Hz, CH_2NH_2), 6.42 (1H, s, dimethylthienyl 4-*H*), 6.50 (1H, s, aminopropylthienyl 4-*H*). δ_C (100 MHz; $CDCl_3$; Me_4Si, 5000 scans) 14.57, 14.63, 14.89 (3 x CH_3), 26.5 ($CH_2CH_2CH_2NH_2$), 29.2 ($CH_2CH_2NH_2$), 47.0 (CH_2NH_2), 109.8 (tm, $^1J_{C\text{-}F}$ = 268 Hz, perfluorocyclopentenyl 4-*C*), 114.7 (tm, $^1J_{C\text{-}F}$ = 254 Hz, perfluorocyclopentenyl 3-*C*, 5-*C*.), 119.8, 120.1 (dimethylthienyl 2-*C*, aminopropylthienyl 2-*C*), 127.4, 128.2 (dimethylthienyl 4-*C*H, aminopropylthienyl 4-*C*H), 132.2, 133.0 (2 x m, perfluorocyclopentenyl 1-*C*, 2-*C*), 140.1, 140.3 (dimethylthienyl 3-*C*, aminopropylthienyl 3-*C*), 143.2 (dimethylthienyl 5-*C*), 147.4 (aminopropylthienyl 5-*C*). δ_F (376 MHz, $CDCl_3$) -131.2 (4-*F*), -109.03, -109.12 (3-*F*, 5-F). *m/z* (ES^+) = 440.0940 ($[M+H]^+$ $C_{19}H_{20}F_6NS_2$ requires 440.0936). *m/z* (CI^+) = 440 ($[M+H]^+$, 5 %), 391 (10 %), 377 (30 %), 154 (41 %), 137 (100 %), 113 (93 %), 58 (78 %). The sample was not pure but the molecular ion was clear. Subsequent derivatisation confirmed the structure beyond reasonable doubt.

4.9.9 *Spreadsheet for the calculation of the spectral overlap integral of 1 and 96.*

λ/ nm	NMA emission intensity	Emission Intensity/ sum of intensities B/38837.6903	Absorbance of B-Form of AMINE	ε/ $dm^3mol^{-1}cm^{-1}$ D/0.0000715	Wavelength^4 nm^4 A^4		J C*E*F
250	0.0	1.96E-14	0.59376	8.30E+03	3.91E+09		6.36E-01
251	0.0	2.31E-14	0.59247	8.29E+03	3.97E+09		7.58E-01
252	0.0	2.71E-14	0.58654	8.20E+03	4.03E+09		8.97E-01
253	0.0	3.19E-14	0.57618	8.06E+03	4.10E+09		1.05E+00
254	0.0	3.75E-14	0.56395	7.89E+03	4.16E+09		1.23E+00
255	0.0	4.42E-14	0.54700	7.65E+03	4.23E+09		1.43E+00
256	0.0	5.20E-14	0.52712	7.37E+03	4.29E+09		1.65E+00
257	0.0	6.11E-14	0.50587	7.08E+03	4.36E+09		1.89E+00
258	0.0	7.19E-14	0.48247	6.75E+03	4.43E+09		2.15E+00
259	0.0	8.46E-14	0.46080	6.44E+03	4.50E+09		2.45E+00
260	0.0	9.96E-14	0.43990	6.15E+03	4.57E+09		2.80E+00
261	0.0	1.17E-13	0.41926	5.86E+03	4.64E+09		3.19E+00
262	0.0	1.38E-13	0.39959	5.59E+03	4.71E+09		3.63E+00
263	0.0	1.62E-13	0.38315	5.36E+03	4.78E+09		4.16E+00
264	0.0	1.91E-13	0.37015	5.18E+03	4.86E+09		4.80E+00

265	0.0	2.24E-13	0.35829	5.01E+03	4.93E+09	5.54E+00
266	0.0	2.64E-13	0.34595	4.84E+03	5.01E+09	6.39E+00
267	0.0	3.11E-13	0.33569	4.69E+03	5.08E+09	7.41E+00
268	0.0	3.65E-13	0.32844	4.59E+03	5.16E+09	8.66E+00
269	0.0	4.30E-13	0.32218	4.51E+03	5.24E+09	1.01E+01
270	0.0	5.06E-13	0.31518	4.41E+03	5.31E+09	1.18E+01
271	0.0	5.95E-13	0.31080	4.35E+03	5.39E+09	1.39E+01
272	0.0	7.00E-13	0.30838	4.31E+03	5.47E+09	1.65E+01
273	0.0	8.23E-13	0.30274	4.23E+03	5.55E+09	1.94E+01
274	0.0	9.69E-13	0.30158	4.22E+03	5.64E+09	2.30E+01
275	0.0	1.14E-12	0.30066	4.21E+03	5.72E+09	2.74E+01
276	0.0	1.34E-12	0.29844	4.17E+03	5.80E+09	3.25E+01
277	0.0	1.58E-12	0.29747	4.16E+03	5.89E+09	3.86E+01
278	0.0	1.86E-12	0.29652	4.15E+03	5.97E+09	4.60E+01
279	0.0	2.18E-12	0.29832	4.17E+03	6.06E+09	5.52E+01
280	0.0	2.57E-12	0.29900	4.18E+03	6.15E+09	6.60E+01
281	0.0	3.02E-12	0.29988	4.19E+03	6.23E+09	7.90E+01
282	0.0	3.56E-12	0.30031	4.20E+03	6.32E+09	9.44E+01
283	0.0	4.18E-12	0.30461	4.26E+03	6.41E+09	1.14E+02
284	0.0	4.92E-12	0.30733	4.30E+03	6.51E+09	1.38E+02
285	0.0	5.79E-12	0.31069	4.35E+03	6.60E+09	1.66E+02
286	0.0	6.81E-12	0.31360	4.39E+03	6.69E+09	2.00E+02
287	0.0	8.01E-12	0.31530	4.41E+03	6.78E+09	2.40E+02
288	0.0	9.43E-12	0.31859	4.46E+03	6.88E+09	2.89E+02
289	0.0	1.11E-11	0.32049	4.48E+03	6.98E+09	3.47E+02
290	0.0	1.30E-11	0.32226	4.51E+03	7.07E+09	4.16E+02
291	0.0	1.53E-11	0.31916	4.46E+03	7.17E+09	4.91E+02
292	0.0	1.81E-11	0.32355	4.53E+03	7.27E+09	5.94E+02
293	0.0	2.12E-11	0.32553	4.55E+03	7.37E+09	7.13E+02
294	0.0	2.50E-11	0.32248	4.51E+03	7.47E+09	8.42E+02
295	0.0	2.94E-11	0.32299	4.52E+03	7.57E+09	1.01E+03
296	0.0	3.46E-11	0.32009	4.48E+03	7.68E+09	1.19E+03
297	0.0	4.07E-11	0.31760	4.44E+03	7.78E+09	1.41E+03
298	0.0	4.79E-11	0.31568	4.42E+03	7.89E+09	1.67E+03
299	0.0	5.63E-11	0.31330	4.38E+03	7.99E+09	1.97E+03
300	0.0	6.63E-11	0.30832	4.31E+03	8.10E+09	2.31E+03
301	0.0	7.80E-11	0.30698	4.29E+03	8.21E+09	2.75E+03
302	0.0	9.17E-11	0.30258	4.23E+03	8.32E+09	3.23E+03
303	0.0	1.08E-10	0.30066	4.21E+03	8.43E+09	3.82E+03
304	0.0	1.27E-10	0.29788	4.17E+03	8.54E+09	4.52E+03
305	0.0	1.49E-10	0.29565	4.13E+03	8.65E+09	5.34E+03
306	0.0	1.76E-10	0.29474	4.12E+03	8.77E+09	6.35E+03
307	0.0	2.07E-10	0.29080	4.07E+03	8.88E+09	7.47E+03
308	0.0	2.43E-10	0.28879	4.04E+03	9.00E+09	8.84E+03
309	0.0	2.86E-10	0.28484	3.98E+03	9.12E+09	1.04E+04
310	0.0	3.37E-10	0.28576	4.00E+03	9.24E+09	1.24E+04
311	0.0	3.96E-10	0.28110	3.93E+03	9.35E+09	1.46E+04
312	0.0	4.66E-10	0.27964	3.91E+03	9.48E+09	1.73E+04
313	0.0	5.48E-10	0.28229	3.95E+03	9.60E+09	2.08E+04
314	0.0	6.45E-10	0.27916	3.90E+03	9.72E+09	2.45E+04
315	0.0	7.59E-10	0.27499	3.85E+03	9.85E+09	2.87E+04
316	0.0	8.93E-10	0.27350	3.83E+03	9.97E+09	3.40E+04
317	0.0	1.05E-09	0.27336	3.82E+03	1.01E+10	4.05E+04
318	0.0	1.24E-09	0.27607	3.86E+03	1.02E+10	4.88E+04

319	0.0	1.45E-09	0.27285	3.82E+03	1.04E+10	5.74E+04
320	0.0	1.71E-09	0.27238	3.81E+03	1.05E+10	6.83E+04
321	0.0	2.01E-09	0.27159	3.80E+03	1.06E+10	8.11E+04
322	0.0	2.37E-09	0.27246	3.81E+03	1.08E+10	9.69E+04
323	0.0	2.78E-09	0.27102	3.79E+03	1.09E+10	1.15E+05
324	0.0	3.28E-09	0.26943	3.77E+03	1.10E+10	1.36E+05
325	0.0	3.85E-09	0.27034	3.78E+03	1.12E+10	1.63E+05
326	0.0	4.53E-09	0.26801	3.75E+03	1.13E+10	1.92E+05
327	0.0	5.33E-09	0.27009	3.78E+03	1.14E+10	2.30E+05
328	0.0	6.27E-09	0.26999	3.78E+03	1.16E+10	2.74E+05
329	0.0	7.38E-09	0.26425	3.70E+03	1.17E+10	3.20E+05
330	0.0	8.68E-09	0.26745	3.74E+03	1.19E+10	3.85E+05
331	0.0	1.02E-08	0.26388	3.69E+03	1.20E+10	4.53E+05
332	0.0	1.20E-08	0.26373	3.69E+03	1.21E+10	5.39E+05
333	0.0	1.41E-08	0.26337	3.68E+03	1.23E+10	6.41E+05
334	0.0	1.66E-08	0.25862	3.62E+03	1.24E+10	7.49E+05
335	0.0	1.96E-08	0.26021	3.64E+03	1.26E+10	8.97E+05
336	0.0	2.30E-08	0.26100	3.65E+03	1.27E+10	1.07E+06
337	0.0	2.71E-08	0.26077	3.65E+03	1.29E+10	1.27E+06
338	0.0	3.19E-08	0.25685	3.59E+03	1.31E+10	1.49E+06
339	0.0	3.75E-08	0.25761	3.60E+03	1.32E+10	1.78E+06
340	0.0	4.41E-08	0.25215	3.53E+03	1.34E+10	2.08E+06
341	0.0	5.19E-08	0.24997	3.50E+03	1.35E+10	2.45E+06
342	0.0	6.11E-08	0.25032	3.50E+03	1.37E+10	2.92E+06
343	0.0	7.18E-08	0.24541	3.43E+03	1.38E+10	3.41E+06
344	0.0	8.45E-08	0.24545	3.43E+03	1.40E+10	4.06E+06
345	0.0	9.94E-08	0.24320	3.40E+03	1.42E+10	4.79E+06
346	0.0	1.17E-07	0.23410	3.27E+03	1.43E+10	5.49E+06
347	0.0	1.38E-07	0.23540	3.29E+03	1.45E+10	6.57E+06
348	0.0	1.62E-07	0.23219	3.25E+03	1.47E+10	7.71E+06
349	0.0	1.90E-07	0.23074	3.23E+03	1.48E+10	9.12E+06
350	0.0	2.24E-07	0.22398	3.13E+03	1.50E+10	1.05E+07
351	0.0	2.64E-07	0.21873	3.06E+03	1.52E+10	1.22E+07
352	0.0	3.10E-07	0.21943	3.07E+03	1.54E+10	1.46E+07
353	0.0	3.65E-07	0.21515	3.01E+03	1.55E+10	1.70E+07
354	0.0	4.29E-07	0.21318	2.98E+03	1.57E+10	2.01E+07
355	0.0	5.05E-07	0.21022	2.94E+03	1.59E+10	2.36E+07
356	0.0	5.94E-07	0.20513	2.87E+03	1.61E+10	2.74E+07
357	0.0	6.99E-07	0.20572	2.88E+03	1.62E+10	3.27E+07
358	0.0	8.22E-07	0.20425	2.86E+03	1.64E+10	3.86E+07
359	0.0	9.67E-07	0.19803	2.77E+03	1.66E+10	4.45E+07
360	0.0	1.14E-06	0.19657	2.75E+03	1.68E+10	5.26E+07
361	0.1	1.34E-06	0.19096	2.67E+03	1.70E+10	6.07E+07
362	0.1	1.58E-06	0.18962	2.65E+03	1.72E+10	7.17E+07
363	0.1	1.85E-06	0.18194	2.54E+03	1.74E+10	8.19E+07
364	0.1	2.18E-06	0.18530	2.59E+03	1.76E+10	9.92E+07
365	0.1	2.57E-06	0.18010	2.52E+03	1.77E+10	1.15E+08
366	0.1	3.02E-06	0.17383	2.43E+03	1.79E+10	1.32E+08
367	0.1	3.55E-06	0.17203	2.41E+03	1.81E+10	1.55E+08
368	0.2	4.18E-06	0.16581	2.32E+03	1.83E+10	1.78E+08
369	0.2	4.91E-06	0.16655	2.33E+03	1.85E+10	2.12E+08
370	0.2	5.78E-06	0.15936	2.23E+03	1.87E+10	2.41E+08
371	0.3	6.80E-06	0.15501	2.17E+03	1.89E+10	2.79E+08
372	0.3	8.00E-06	0.14809	2.07E+03	1.92E+10	3.17E+08

373	0.4	9.41E-06	0.15009	2.10E+03	1.94E+10	3.82E+08
374	0.4	1.11E-05	0.15039	2.10E+03	1.96E+10	4.56E+08
375	0.5	1.30E-05	0.14464	2.02E+03	1.98E+10	5.21E+08
376	0.6	1.53E-05	0.14889	2.08E+03	2.00E+10	6.38E+08
377	0.7	1.80E-05	0.14271	2.00E+03	2.02E+10	7.27E+08
378	0.8	2.12E-05	0.13962	1.95E+03	2.04E+10	8.46E+08
379	1.0	2.50E-05	0.13316	1.86E+03	2.06E+10	9.59E+08
380	1.1	2.94E-05	0.12948	1.81E+03	2.09E+10	1.11E+09
381	1.3	3.45E-05	0.13971	1.95E+03	2.11E+10	1.42E+09
382	1.6	4.06E-05	0.13666	1.91E+03	2.13E+10	1.65E+09
383	1.9	4.78E-05	0.13310	1.86E+03	2.15E+10	1.92E+09
384	2.2	5.63E-05	0.13361	1.87E+03	2.17E+10	2.29E+09
385	2.6	6.62E-05	0.14361	2.01E+03	2.20E+10	2.92E+09
386	3.0	7.79E-05	0.14103	1.97E+03	2.22E+10	3.41E+09
387	3.6	9.16E-05	0.14550	2.03E+03	2.24E+10	4.18E+09
388	4.2	1.08E-04	0.14189	1.98E+03	2.27E+10	4.85E+09
389	4.9	1.27E-04	0.14510	2.03E+03	2.29E+10	5.89E+09
390	5.8	1.49E-04	0.14852	2.08E+03	2.31E+10	7.17E+09
391	6.8	1.75E-04	0.14516	2.03E+03	2.34E+10	8.33E+09
392	8.0	2.06E-04	0.15469	2.16E+03	2.36E+10	1.05E+10
393	9.4	2.43E-04	0.15585	2.18E+03	2.39E+10	1.26E+10
394	11.1	2.86E-04	0.15308	2.14E+03	2.41E+10	1.47E+10
395	13.1	3.36E-04	0.16245	2.27E+03	2.43E+10	1.86E+10
396	15.3	3.93E-04	0.16451	2.30E+03	2.46E+10	2.22E+10
397	18.4	4.74E-04	0.16671	2.33E+03	2.48E+10	2.75E+10
398	23.1	5.96E-04	0.16531	2.31E+03	2.51E+10	3.45E+10
399	29.3	7.55E-04	0.17762	2.48E+03	2.53E+10	4.76E+10
400	36.9	9.49E-04	0.17914	2.51E+03	2.56E+10	6.09E+10
401	46.2	1.19E-03	0.18088	2.53E+03	2.59E+10	7.78E+10
402	58.1	1.50E-03	0.18014	2.52E+03	2.61E+10	9.84E+10
403	72.7	1.87E-03	0.18728	2.62E+03	2.64E+10	1.29E+11
404	89.2	2.30E-03	0.19192	2.68E+03	2.66E+10	1.64E+11
405	108.1	2.78E-03	0.20209	2.83E+03	2.69E+10	2.12E+11
406	130.7	3.37E-03	0.20073	2.81E+03	2.72E+10	2.57E+11
407	156.1	4.02E-03	0.20222	2.83E+03	2.74E+10	3.12E+11
408	183.2	4.72E-03	0.21127	2.95E+03	2.77E+10	3.86E+11
409	212.7	5.48E-03	0.21042	2.94E+03	2.80E+10	4.51E+11
410	244.1	6.29E-03	0.21515	3.01E+03	2.83E+10	5.34E+11
411	279.1	7.19E-03	0.21729	3.04E+03	2.85E+10	6.23E+11
412	317.4	8.17E-03	0.22116	3.09E+03	2.88E+10	7.28E+11
413	355.7	9.16E-03	0.22610	3.16E+03	2.91E+10	8.43E+11
414	395.0	1.02E-02	0.22943	3.21E+03	2.94E+10	9.59E+11
415	436.0	1.12E-02	0.23160	3.24E+03	2.97E+10	1.08E+12
416	476.8	1.23E-02	0.23886	3.34E+03	2.99E+10	1.23E+12
417	516.5	1.33E-02	0.24602	3.44E+03	3.02E+10	1.38E+12
418	556.8	1.43E-02	0.24377	3.41E+03	3.05E+10	1.49E+12
419	598.8	1.54E-02	0.24741	3.46E+03	3.08E+10	1.64E+12
420	635.6	1.64E-02	0.24781	3.47E+03	3.11E+10	1.77E+12
421	661.7	1.70E-02	0.25446	3.56E+03	3.14E+10	1.90E+12
422	680.1	1.75E-02	0.25231	3.53E+03	3.17E+10	1.96E+12
423	694.4	1.79E-02	0.25782	3.61E+03	3.20E+10	2.06E+12
424	706.5	1.82E-02	0.25914	3.62E+03	3.23E+10	2.13E+12
425	716.6	1.85E-02	0.25921	3.63E+03	3.26E+10	2.18E+12
426	721.6	1.86E-02	0.26221	3.67E+03	3.29E+10	2.24E+12

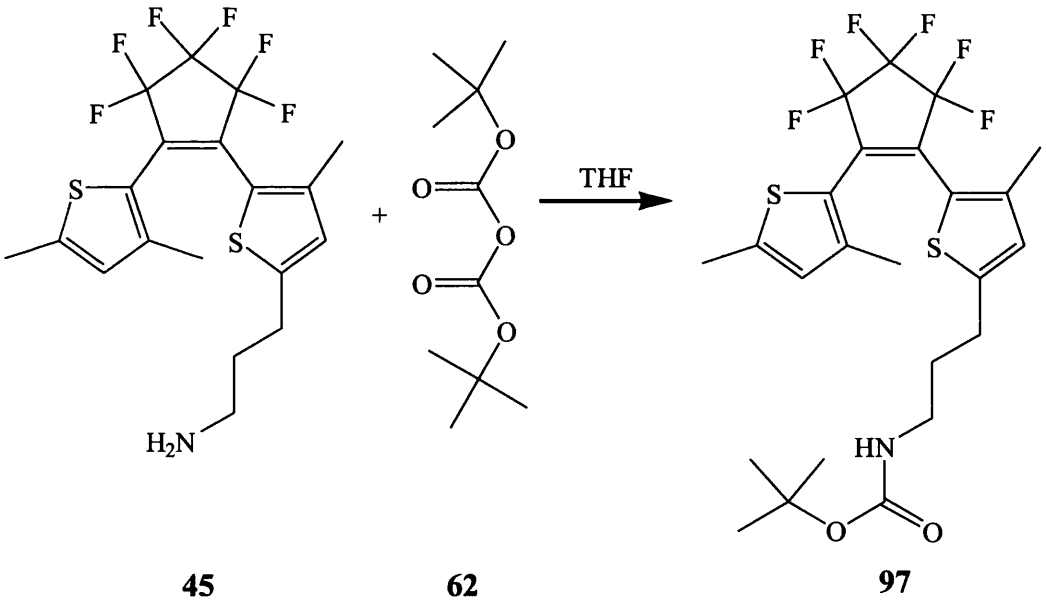
427	720.5	1.86E-02	0.26530	3.71E+03	3.32E+10	2.29E+12
428	714.9	1.84E-02	0.26668	3.73E+03	3.36E+10	2.30E+12
429	705.9	1.82E-02	0.26791	3.75E+03	3.39E+10	2.31E+12
430	697.9	1.80E-02	0.26912	3.76E+03	3.42E+10	2.31E+12
431	691.2	1.78E-02	0.27042	3.78E+03	3.45E+10	2.32E+12
432	683.6	1.76E-02	0.27177	3.80E+03	3.48E+10	2.33E+12
433	673.6	1.73E-02	0.26968	3.77E+03	3.52E+10	2.30E+12
434	663.1	1.71E-02	0.27049	3.78E+03	3.55E+10	2.29E+12
435	655.6	1.69E-02	0.26861	3.76E+03	3.58E+10	2.27E+12
436	649.0	1.67E-02	0.27026	3.78E+03	3.61E+10	2.28E+12
437	641.6	1.65E-02	0.26988	3.77E+03	3.65E+10	2.27E+12
438	636.3	1.64E-02	0.27062	3.78E+03	3.68E+10	2.28E+12
439	633.0	1.63E-02	0.26864	3.76E+03	3.71E+10	2.27E+12
440	629.3	1.62E-02	0.26465	3.70E+03	3.75E+10	2.25E+12
441	626.7	1.61E-02	0.26480	3.70E+03	3.78E+10	2.26E+12
442	625.5	1.61E-02	0.26129	3.65E+03	3.82E+10	2.25E+12
443	622.7	1.60E-02	0.25886	3.62E+03	3.85E+10	2.24E+12
444	617.6	1.59E-02	0.25873	3.62E+03	3.89E+10	2.24E+12
445	610.6	1.57E-02	0.25660	3.59E+03	3.92E+10	2.21E+12
446	603.0	1.55E-02	0.25126	3.51E+03	3.96E+10	2.16E+12
447	595.8	1.53E-02	0.24642	3.45E+03	3.99E+10	2.11E+12
448	588.2	1.51E-02	0.24910	3.48E+03	4.03E+10	2.13E+12
449	578.1	1.49E-02	0.24576	3.44E+03	4.06E+10	2.08E+12
450	566.0	1.46E-02	0.24120	3.37E+03	4.10E+10	2.02E+12
451	552.7	1.42E-02	0.23809	3.33E+03	4.14E+10	1.96E+12
452	536.7	1.38E-02	0.23278	3.26E+03	4.17E+10	1.88E+12
453	519.1	1.34E-02	0.22831	3.19E+03	4.21E+10	1.80E+12
454	500.9	1.29E-02	0.22626	3.16E+03	4.25E+10	1.73E+12
455	482.0	1.24E-02	0.22110	3.09E+03	4.29E+10	1.64E+12
456	463.3	1.19E-02	0.21530	3.01E+03	4.32E+10	1.55E+12
457	445.5	1.15E-02	0.21227	2.97E+03	4.36E+10	1.49E+12
458	429.9	1.11E-02	0.20787	2.91E+03	4.40E+10	1.42E+12
459	417.2	1.07E-02	0.20318	2.84E+03	4.44E+10	1.35E+12
460	403.3	1.04E-02	0.19665	2.75E+03	4.48E+10	1.28E+12
461	386.2	9.94E-03	0.19086	2.67E+03	4.52E+10	1.20E+12
462	367.7	9.47E-03	0.18647	2.61E+03	4.56E+10	1.12E+12
463	350.3	9.02E-03	0.18005	2.52E+03	4.60E+10	1.04E+12
464	336.2	8.66E-03	0.17443	2.44E+03	4.64E+10	9.79E+11
465	325.5	8.38E-03	0.16953	2.37E+03	4.68E+10	9.29E+11
466	313.9	8.08E-03	0.16330	2.28E+03	4.72E+10	8.70E+11
467	300.2	7.73E-03	0.15929	2.23E+03	4.76E+10	8.19E+11
468	287.5	7.40E-03	0.15406	2.15E+03	4.80E+10	7.65E+11
469	276.4	7.12E-03	0.14648	2.05E+03	4.84E+10	7.06E+11
470	266.5	6.86E-03	0.13975	1.95E+03	4.88E+10	6.54E+11
471	257.9	6.64E-03	0.13611	1.90E+03	4.92E+10	6.22E+11
472	250.2	6.44E-03	0.12827	1.79E+03	4.96E+10	5.74E+11
473	242.2	6.24E-03	0.12465	1.74E+03	5.01E+10	5.44E+11
474	233.8	6.02E-03	0.11850	1.66E+03	5.05E+10	5.04E+11
475	225.3	5.80E-03	0.11140	1.56E+03	5.09E+10	4.60E+11
476	217.4	5.60E-03	0.10663	1.49E+03	5.13E+10	4.28E+11
477	210.1	5.41E-03	0.10191	1.43E+03	5.18E+10	3.99E+11
478	203.6	5.24E-03	0.09554	1.34E+03	5.22E+10	3.66E+11
479	196.9	5.07E-03	0.08951	1.25E+03	5.26E+10	3.34E+11
480	189.4	4.88E-03	0.08564	1.20E+03	5.31E+10	3.10E+11

481	181.9	4.68E-03	0.08190	1.15E+03	5.35E+10	2.87E+11
482	174.6	4.50E-03	0.07627	1.07E+03	5.40E+10	2.59E+11
483	166.7	4.29E-03	0.07435	1.04E+03	5.44E+10	2.43E+11
484	159.4	4.10E-03	0.06673	9.33E+02	5.49E+10	2.10E+11
485	153.2	3.94E-03	0.06414	8.97E+02	5.53E+10	1.96E+11
486	146.7	3.78E-03	0.05956	8.33E+02	5.58E+10	1.76E+11
487	139.2	3.58E-03	0.05444	7.61E+02	5.62E+10	1.54E+11
488	131.2	3.38E-03	0.05208	7.28E+02	5.67E+10	1.40E+11
489	123.8	3.19E-03	0.04715	6.59E+02	5.72E+10	1.20E+11
490	117.8	3.03E-03	0.04457	6.23E+02	5.76E+10	1.09E+11
491	112.4	2.89E-03	0.04171	5.83E+02	5.81E+10	9.81E+10
492	107.0	2.76E-03	0.03916	5.48E+02	5.86E+10	8.84E+10
493	101.9	2.62E-03	0.03579	5.01E+02	5.91E+10	7.76E+10
494	96.8	2.49E-03	0.03344	4.68E+02	5.96E+10	6.94E+10
495	91.3	2.35E-03	0.03186	4.46E+02	6.00E+10	6.29E+10
496	86.5	2.23E-03	0.02906	4.06E+02	6.05E+10	5.48E+10
497	82.2	2.12E-03	0.02636	3.69E+02	6.10E+10	4.76E+10
498	78.2	2.01E-03	0.02574	3.60E+02	6.15E+10	4.46E+10
499	74.5	1.92E-03	0.02374	3.32E+02	6.20E+10	3.95E+10
500	71.1	1.83E-03	0.02008	2.81E+02	6.25E+10	3.21E+10
501	67.7	1.74E-03	0.01935	2.71E+02	6.30E+10	2.97E+10
502	64.5	1.66E-03	0.01786	2.50E+02	6.35E+10	2.64E+10
503	61.2	1.57E-03	0.01667	2.33E+02	6.40E+10	2.35E+10
504	57.8	1.49E-03	0.01534	2.15E+02	6.45E+10	2.06E+10
505	55.1	1.42E-03	0.01343	1.88E+02	6.50E+10	1.73E+10
506	53.2	1.37E-03	0.01225	1.71E+02	6.56E+10	1.54E+10
507	51.6	1.33E-03	0.01246	1.74E+02	6.61E+10	1.53E+10
508	49.7	1.28E-03	0.01121	1.57E+02	6.66E+10	1.34E+10
509	47.2	1.22E-03	0.01082	1.51E+02	6.71E+10	1.23E+10
510	44.9	1.16E-03	0.00881	1.23E+02	6.77E+10	9.65E+09
511	43.6	1.12E-03	0.00817	1.14E+02	6.82E+10	8.75E+09
512	42.1	1.08E-03	0.00784	1.10E+02	6.87E+10	8.17E+09
513	39.7	1.02E-03	0.00743	1.04E+02	6.93E+10	7.35E+09
514	37.1	9.56E-04	0.00585	8.18E+01	6.98E+10	5.46E+09
515	34.9	9.00E-04	0.00581	8.12E+01	7.03E+10	5.14E+09
516	33.0	8.50E-04	0.00494	6.91E+01	7.09E+10	4.16E+09
517	31.3	8.05E-04	0.00431	6.02E+01	7.14E+10	3.46E+09
518	29.8	7.67E-04	0.00516	7.22E+01	7.20E+10	3.98E+09
519	28.2	7.26E-04	0.00323	4.52E+01	7.26E+10	2.38E+09
520	26.4	6.79E-04	0.00397	5.55E+01	7.31E+10	2.76E+09
521	24.8	6.38E-04	0.00242	3.39E+01	7.37E+10	1.59E+09
522	23.4	6.03E-04	0.00378	5.29E+01	7.42E+10	2.37E+09
523	22.2	5.71E-04	0.00452	6.33E+01	7.48E+10	2.70E+09
524	21.1	5.43E-04	0.00233	3.26E+01	7.54E+10	1.33E+09
525	20.0	5.16E-04	0.00262	3.66E+01	7.60E+10	1.43E+09
526	18.9	4.86E-04	0.00222	3.10E+01	7.65E+10	1.15E+09
527	17.8	4.57E-04	0.00128	1.79E+01	7.71E+10	6.31E+08
528	16.9	4.35E-04	0.00253	3.54E+01	7.77E+10	1.20E+09
529	16.2	4.17E-04	0.00240	3.35E+01	7.83E+10	1.10E+09
530	15.4	3.96E-04	0.00242	3.39E+01	7.89E+10	1.06E+09
531	14.4	3.71E-04	0.00121	1.69E+01	7.95E+10	4.99E+08
532	13.7	3.52E-04	0.00046	6.45E+00	8.01E+10	1.82E+08
533	13.0	3.34E-04	0.00000	0.00E+00	8.07E+10	0.00E+00
534	12.3	3.17E-04	0.00191	2.67E+01	8.13E+10	6.88E+08

535	11.4	2.93E-04	0.00072	1.01E+01	8.19E+10	2.43E+08
536	10.3	2.66E-04	0.00139	1.95E+01	8.25E+10	4.27E+08
537	9.6	2.47E-04	0.00175	2.44E+01	8.32E+10	5.01E+08
538	9.2	2.37E-04	0.00106	1.48E+01	8.38E+10	2.95E+08
539	9.0	2.31E-04	0.00055	7.68E+00	8.44E+10	1.49E+08
540	8.6	2.23E-04	0.00153	2.15E+01	8.50E+10	4.06E+08
541	8.3	2.14E-04	0.00127	1.78E+01	8.57E+10	3.26E+08
542	8.0	2.06E-04	0.00000	0.00E+00	8.63E+10	0.00E+00
543	7.7	1.97E-04	0.00057	8.03E+00	8.69E+10	1.38E+08
544	7.3	1.87E-04	0.00013	1.81E+00	8.76E+10	2.96E+07
545	6.9	1.78E-04	0.00008	1.13E+00	8.82E+10	1.77E+07
546	6.6	1.70E-04	0.00070	9.84E+00	8.89E+10	1.49E+08
547	6.3	1.62E-04	0.00018	2.49E+00	8.95E+10	3.62E+07
548	6.1	1.56E-04	0.00000	0.00E+00	9.02E+10	0.00E+00
549	5.9	1.52E-04	0.00087	1.22E+01	9.08E+10	1.69E+08
550	5.8	1.48E-04	0.00064	8.96E+00	9.15E+10	1.22E+08
551	5.8	1.48E-04	0.00070	9.76E+00	9.22E+10	1.33E+08
552	5.8	1.48E-04	0.00003	3.89E-01	9.28E+10	5.36E+06
553	5.8	1.48E-04	0.00044	6.18E+00	9.35E+10	8.57E+07
554	5.8	1.48E-04	0.00000	0.00E+00	9.42E+10	0.00E+00
555	5.8	1.48E-04	0.00013	1.80E+00	9.49E+10	2.53E+07
556	5.8	1.48E-04	0.00002	2.42E-01	9.56E+10	3.42E+06
557	5.8	1.48E-04	0.00029	4.01E+00	9.63E+10	5.73E+07
558	5.8	1.48E-04	0.00075	1.05E+01	9.69E+10	1.51E+08
559	5.8	1.48E-04	0.00059	8.28E+00	9.76E+10	1.20E+08
560	5.8	1.48E-04	0.00000	0.00E+00	9.83E+10	0.00E+00
561	5.8	1.48E-04	0.00000	0.00E+00	9.90E+10	0.00E+00
562	5.8	1.48E-04	0.00107	1.49E+01	9.98E+10	2.21E+08
563	5.8	1.48E-04	0.00021	2.98E+00	1.00E+11	4.44E+07
564	5.8	1.48E-04	0.00000	0.00E+00	1.01E+11	0.00E+00
565	5.8	1.48E-04	0.00020	2.84E+00	1.02E+11	4.30E+07
566	5.8	1.48E-04	0.00000	0.00E+00	1.03E+11	0.00E+00
567	5.8	1.48E-04	0.00080	1.12E+01	1.03E+11	1.72E+08
568	5.8	1.48E-04	0.00000	0.00E+00	1.04E+11	0.00E+00
569	5.8	1.48E-04	0.00025	3.55E+00	1.05E+11	5.52E+07
570	5.8	1.48E-04	0.00086	1.21E+01	1.06E+11	1.89E+08
571	5.8	1.48E-04	0.00023	3.26E+00	1.06E+11	5.14E+07
572	5.8	1.48E-04	0.00064	8.92E+00	1.07E+11	1.42E+08
573	5.8	1.48E-04	0.00007	9.39E-01	1.08E+11	1.50E+07
574	5.8	1.48E-04	0.00000	0.00E+00	1.09E+11	0.00E+00
575	5.8	1.48E-04	0.00014	1.95E+00	1.09E+11	3.16E+07
576	5.8	1.48E-04	0.00000	0.00E+00	1.10E+11	0.00E+00
577	5.8	1.48E-04	0.00000	0.00E+00	1.11E+11	0.00E+00
578	5.8	1.48E-04	0.00000	0.00E+00	1.12E+11	0.00E+00
579	5.8	1.48E-04	0.00000	0.00E+00	1.12E+11	0.00E+00
580	5.8	1.48E-04	0.00055	7.66E+00	1.13E+11	1.28E+08
581	5.8	1.48E-04	0.00103	1.44E+01	1.14E+11	2.44E+08
582	5.8	1.48E-04	0.00073	1.03E+01	1.15E+11	1.75E+08
583	5.8	1.48E-04	0.00069	9.68E+00	1.16E+11	1.66E+08
584	5.8	1.48E-04	0.00048	6.69E+00	1.16E+11	1.15E+08
585	5.8	1.48E-04	0.00056	7.77E+00	1.17E+11	1.35E+08
586	5.8	1.48E-04	0.00048	6.76E+00	1.18E+11	1.18E+08
587	5.8	1.48E-04	0.00032	4.46E+00	1.19E+11	7.85E+07
588	5.8	1.48E-04	0.00061	8.54E+00	1.20E+11	1.51E+08

589	5.8	1.48E-04	0.00073	1.02E+01	1.20E+11		1.82E+08
590	5.8	1.48E-04	0.00067	9.31E+00	1.21E+11		1.67E+08
591	5.8	1.48E-04	0.00084	1.18E+01	1.22E+11		2.13E+08
592	5.8	1.48E-04	0.00000	0.00E+00	1.23E+11		0.00E+00
593	5.8	1.48E-04	0.00005	6.95E-01	1.24E+11		1.27E+07
594	5.8	1.48E-04	0.00000	0.00E+00	1.24E+11		0.00E+00
595	5.8	1.48E-04	0.00037	5.18E+00	1.25E+11		9.63E+07
596	5.8	1.48E-04	0.00056	7.79E+00	1.26E+11		1.46E+08
597	5.8	1.48E-04	0.00053	7.48E+00	1.27E+11		1.41E+08
598	5.8	1.48E-04	0.00028	3.93E+00	1.28E+11		7.46E+07
599	5.8	1.48E-04	0.00027	3.74E+00	1.29E+11		7.14E+07
600	5.8	1.48E-04	0.00042	5.91E+00	1.30E+11		1.14E+08
	SUM 39,837.6903	SUM 1.0			Spectral Overlap integral $dm^3mol^{-1}cm^{-1}nm^4$ Forster Distance Angstroms	J Ro	1.13E+14 35.3

4.9.10 *Boc protection of 45.*



45 **62** **97**

Scheme 4.21: Protection of 45 as the Boc derivative 97 by reaction with 62 in THF.

Di-*tert*-butyl dicarbonate (**62**, 0.017 g, 0.078 mmol) was dissolved in dry, distilled THF (10 mL) in a 50 mL round-bottomed flask. 1-([3-Methyl-5-(3-amino-1-propyl)]-2-thienyl)-2-(3,5-dimethyl-2-thienyl)perfluorocyclopentene (**45**, 0.031 g, 0.071 mmol dissolved in 5 mL THF) was added dropwise and the solution was stirred overnight. The stirrer was removed from the solution and then the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (20 mL), and the resulting solution

was washed with saturated aqueous sodium bicarbonate solution (15 mL), 5% aqueous potassium hydrogen sulfate solution (15 mL) and water (15 mL) and then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (alumina, 5% ethyl acetate/hexane). The product, (3-{5-[2-(3,5-dimethyl-2-thienyl)perfluorocyclopent-1-enyl]-4-methyl-2-thienyl}propyl)carbamic acid tert-butyl ester (**97**), was isolated as a dark yellow gum in 85 % yield (0.033 g, 0.060 mmol). The gum was observed to solidify over a number of days. The resulting yellow solid was recrystallised (Et_2O/hexane) to give yellow crystals (mp 89.8-91.1 °C). ν_{max} (film) /cm^{-1} 1667.3 (C=O). λ_{max} (MeOH)/nm 344 (ε/$dm^3mol^{-1}cm^{-1}$ 1.15 x 10^4). After irradiation with light at 366 nm for 15 minutes: 437 (4.34 x 10^3). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.36 (9H, s, C(CH_3)$_3$), 1.61, 1.63 (3H, s, dimethylthienyl 3-CH_3, 3H, s, aminopropylthienyl 3-CH_3), 1.71 (2H, quintet, J = 8 Hz, CH_2CH_2NH), 2.39 (3H, s, dimethylthienyl 5-CH_3), 2.72 (2H, t, J = 8 Hz $CH_2CH_2CH_2NH$), 3.10 (2H, m, CH_2NH), 4.51 (1H, s, D_2O Ex., N*H*), 6.42, 6.48 (1H, s, dimethylthienyl 4-*H*, 1H, s, aminopropylthienyl 4-*H*). δ_C (100 MHz; $CDCl_3$; Me_4Si, 5000 scans) 15.57, 15.64, 15.73 (3 x CH_3), 27.7 ($CH_2CH_2CH_2NH$), 28.8 (C(CH_3)$_3$), 32.0 ($CH_2CH_2NH_2$), 40.3 (CH_2NH_2), 79.7 (C(CH_3)$_3$), 111.2 (tm, $^1J_{C\text{-}F}$ = 268 Hz, perfluorocyclopentenyl 4-*C*), 116.0 (tm, $^1J_{C\text{-}F}$ = 254 Hz, perfluorocyclopentenyl 3-*C*, 5-*C*.), 121.3, 121.4 (dimethylthienyl 2-*C*, aminopropylthienyl 2-*C*), 129.7, 130.2 (dimethylthienyl 4-CH, aminopropylthienyl 4-*C*H), 133.8 (m, perfluorocyclopentenyl 1-*C*, 2-*C*), 141.5, 141.7 (dimethylthienyl 3-*C*, aminopropylthienyl 3-*C*), 144.6 (dimethylthienyl 5-C), 149.0 (aminopropylthienyl 5-*C*), 156.4 (*C*=O). δ_F (376 MHz, $CDCl_3$) -131.2 (4-*F*), -109.12, -109.05 (3-*F*, 5-*F*). *m/z* (ES^+) = 562.1272 ($[M+Na]^+$ $C_{24}H_{27}F_6O_2NS_2Na$ requires 562.1280). *m/z* (EI^+) = 539.1 ($[M]^+$ 100 %), 521 (27 %), 503 (22 %), 483 ($[M\text{-}C(CH_3)_3]^+$ 15%), 57 ($[C(CH_3)_3]^+$ 100 %). *m/z* (CI^+) 557 ($[M+NH_4]^+$ 32 %), 540 ($[M+H]^+$ 9 %), 501 (100 %), 453 (56 %), 343 (60 %), 318.4 (50 %), 170 (29 %).

Deprotection 1: A sample of the product (0.032 g, 0.0593 mmol) was refluxed with conc. HCl (0.3 mL) in methanol (3 mL) at 85 °C for 2 hours. The solvent was removed under reduced pressure. *m/z* (ES^+) = 440.0934 ($[M+H]^+$ $C_{19}H_{20}F_6NS_2$ requires 440.0936).

Deprotection 2: A sample of the product (0.012 g, 0.0223 mmol) was stirred with trifluoroacetic acid (0.5 mL) in dichloromethane (0.5 mL) for 4 hours. The solvent was removed under reduced pressure. Ethanol (0.5 mL) and water (0.5 mL) were added and the solvents were removed under reduced pressure. *m/z* (ES^+) = 440.0940 ($[M+H]^+$ $C_{19}H_{20}F_6NS_2$ requires 440.0936).

Conclusion.

Conclusion

The compound 1,2-*bis*-(3,5-dimethyl-2-thienyl)perfluorocyclopentene (**21**) was found in the literature and appeared to have a closed form (**22**) that would quench the fluorescence of *N*-methylacridone (**1**) through resonance energy transfer (RET).

In order to synthesise **21** it was necessary to develop a method for the high-yielding regioselective synthesis of 2,4-dimethylthiophene (**23**). This was achieved *via* regioselective 5-lithiation of 3-methylthiophene (**38**) with lithium 2,2,6,6-tetramethylpiperidide (**69**) and subsequent reaction with iodomethane. The replacement of iodomethane with a range of electrophiles afforded several selectively-synthesised products which were either novel or had not previously been synthesised in such high selectivity and high yield.

Compound **21** was synthesised and Förster calculations showed that the closed form **22** would be a viable RET acceptor for the fluorescence of compound **1**.

Molecule **45**, a modified version of **21** containing a propylamino linker group was designed, and synthetic routes were planned starting from some of the products of the regioselective lithiation of **38** and reaction with electrophiles.

The first route, involving the reaction of several protected derivatives of 3-(4-methyl-2-thienyl)-1-propylamine (**47**) was unsuccessful, but several novel compounds were synthesised in the attempt.

The second route, involving the synthesis and subsequent functionalisation of a modified version of **21** containing an aldehyde group, was successful and **45** was synthesised *via* several novel compounds, most of which were photochromic. The closed form of **45** was shown to be a viable RET acceptor for compound **1**.

Further work would involve the synthesis of a modified version of the fluorophore **1** containing an *N*-hydroxysuccinimide ester linkage at the end of a 1,3-propyl chain. The so modified donor should then be linked easily to compound **45**, and the practical effectiveness of the proposed switchable donor-acccceptor pair could be observed. The switchable fluorescence effect could be observed in a variety of media including in solution and on thin films.

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Appendix:

X-Ray crystallographic data for Compound 66.

Table 1. Crystal data and structure refinement.

Identification code	**2006src0607**	
Empirical formula	$C_{19}H_{16}F_6O_2S_2$	
Formula weight	454.44	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*Pbca*	
Unit cell dimensions	$a = 8.8049(3)$ Å	$\alpha = 90°$
	$b = 11.3731(3)$ Å	$\beta = 90°$
	$c = 37.8441(11)$ Å	$\gamma = 90°$
Volume	3789.7(2) Å^3	
Z	8	
Density (calculated)	1.593 Mg / m^3	
Absorption coefficient	0.352 mm^{-1}	
F(000)	1856	
Crystal	Fragment; colourless	
Crystal size	0.12 × 0.10 × 0.05 mm^3	
θ range for data collection	2.97 – 27.50°	
Index ranges	$-11 \le h \le 10$, $-12 \le k \le 14$, $-48 \le l \le 44$	
Reflections collected	13711	
Independent reflections	4047 [$R_{int} = 0.0435$]	
Completeness to $\theta = 27.50°$	92.9 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9826 and 0.9590	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4047 / 0 / 265	
Goodness-of-fit on F^2	1.105	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0583$, $wR2 = 0.1636$	
R indices (all data)	$R1 = 0.0897$, $wR2 = 0.1958$	
Largest diff. peak and hole	0.508 and –0.607 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	−1621(4)	5627(3)	2668(1)	21(1)	1
C2	−639(4)	4736(3)	2176(1)	26(1)	1
C3	−1486(5)	3860(4)	2400(1)	41(1)	1
C4	−1140(4)	6316(3)	2983(1)	21(1)	1
C5	−1851(4)	7258(3)	3130(1)	21(1)	1
C6	−1037(4)	7779(3)	3411(1)	19(1)	1
C7	−1557(4)	8889(3)	3596(1)	24(1)	1
C8	285(4)	7174(3)	3482(1)	20(1)	1
C9	1433(4)	7452(3)	3748(1)	20(1)	1
C10	3079(4)	7411(3)	3647(1)	25(1)	1
C11	3946(4)	7699(3)	3988(1)	26(1)	1
C12	2758(4)	8304(3)	4217(1)	23(1)	1
C13	1261(4)	7849(3)	4082(1)	19(1)	1
C14	−84(4)	7902(3)	4306(1)	22(1)	1
C15	−1267(4)	7100(3)	4328(1)	21(1)	1
C16	−1384(4)	5983(3)	4123(1)	27(1)	1
C17	−2372(4)	7466(3)	4578(1)	22(1)	1
C18	−2063(4)	8496(3)	4744(1)	23(1)	1
C19	−3011(4)	9140(3)	5012(1)	31(1)	1
O1	−585(3)	5793(2)	2385(1)	27(1)	1
O2	−1572(3)	4410(2)	2740(1)	30(1)	1
F1	3517(2)	6346(2)	3520(1)	37(1)	1
F2	3433(2)	8199(2)	3393(1)	39(1)	1
F3	5192(2)	8345(2)	3934(1)	37(1)	1
F4	4382(2)	6683(2)	4147(1)	34(1)	1
F5	2863(2)	9497(2)	4174(1)	30(1)	1
F6	3013(2)	8103(2)	4565(1)	33(1)	1
S1	534(1)	6007(1)	3193(1)	22(1)	1
S2	−368(1)	9068(1)	4595(1)	23(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1-O2	1.411(4)	C10-F1	1.360(4)
C1-O1	1.420(4)	C10-C11	1.533(5)
C1-C4	1.487(5)	C11-F3	1.336(4)
C2-O1	1.440(4)	C11-F4	1.358(4)
C2-C3	1.507(5)	C11-C12	1.524(5)
C3-O2	1.433(4)	C12-F6	1.357(4)
C4-C5	1.361(5)	C12-F5	1.369(4)
C4-S1	1.712(3)	C12-C13	1.505(4)
C5-C6	1.413(5)	C13-C14	1.458(5)
C6-C8	1.379(5)	C14-C15	1.387(5)
C6-C7	1.514(5)	C14-S2	1.736(4)
C8-C9	1.461(5)	C15-C17	1.420(5)
C8-S1	1.734(3)	C15-C16	1.492(5)
C9-C13	1.351(5)	C17-C18	1.356(5)
C9-C10	1.499(5)	C18-C19	1.504(5)
C10-F2	1.352(4)	C18-S2	1.723(4)
O2-C1-O1	104.9(3)	F3-C11-C10	113.5(3)
O2-C1-C4	110.7(3)	F4-C11-C10	109.3(3)
O1-C1-C4	110.6(3)	C12-C11-C10	103.4(3)
O1-C2-C3	105.0(3)	F6-C12-F5	105.7(3)
O2-C3-C2	104.1(3)	F6-C12-C13	114.6(3)
C5-C4-C1	127.7(3)	F5-C12-C13	111.1(3)
C5-C4-S1	111.5(2)	F6-C12-C11	111.3(3)
C1-C4-S1	120.7(3)	F5-C12-C11	109.5(3)
C4-C5-C6	113.9(3)	C13-C12-C11	104.7(3)
C8-C6-C5	111.4(3)	C9-C13-C14	130.5(3)
C8-C6-C7	125.6(3)	C9-C13-C12	109.5(3)
C5-C6-C7	122.9(3)	C14-C13-C12	120.0(3)
C6-C8-C9	127.6(3)	C15-C14-C13	128.1(3)
C6-C8-S1	111.5(2)	C15-C14-S2	110.9(2)
C9-C8-S1	120.9(2)	C13-C14-S2	121.0(2)
C13-C9-C8	129.8(3)	C14-C15-C17	111.2(3)
C13-C9-C10	110.9(3)	C14-C15-C16	125.6(3)
C8-C9-C10	119.1(3)	C17-C15-C16	123.3(3)
F2-C10-F1	105.8(3)	C18-C17-C15	115.1(3)
F2-C10-C9	112.5(3)	C17-C18-C19	128.4(3)
F1-C10-C9	113.1(3)	C17-C18-S2	110.4(3)
F2-C10-C11	110.0(3)	C19-C18-S2	121.1(3)
F1-C10-C11	110.3(3)	C1-O1-C2	106.4(3)
C9-C10-C11	105.1(3)	C1-O2-C3	104.9(3)
F3-C11-F4	107.7(3)	C4-S1-C8	91.58(16)
F3-C11-C12	113.7(3)	C18-S2-C14	92.40(17)
F4-C11-C12	109.0(3)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [Å^2 × 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	22(2)	22(2)	18(2)	−1(1)	0(1)	−1(1)
C2	32(2)	30(2)	16(2)	−6(2)	1(1)	2(2)
C3	68(3)	29(2)	25(2)	−11(2)	5(2)	−8(2)
C4	29(2)	18(2)	15(2)	2(1)	−1(1)	−1(1)
C5	20(2)	23(2)	20(2)	3(1)	0(1)	1(1)
C6	23(2)	18(2)	17(2)	2(1)	1(1)	0(1)
C7	28(2)	22(2)	22(2)	0(2)	−1(1)	5(1)
C8	21(2)	23(2)	14(2)	1(1)	2(1)	1(1)
C9	19(2)	18(2)	23(2)	0(1)	2(1)	1(1)
C10	27(2)	23(2)	25(2)	1(2)	6(1)	0(1)
C11	20(2)	25(2)	35(2)	1(2)	−3(1)	−1(1)
C12	23(2)	22(2)	23(2)	−2(2)	−3(1)	−5(1)
C13	23(2)	13(2)	19(2)	−3(1)	1(1)	−2(1)
C14	21(2)	22(2)	22(2)	2(2)	−3(1)	2(1)
C15	24(2)	24(2)	16(2)	3(1)	−2(1)	1(1)
C16	34(2)	23(2)	24(2)	−1(2)	4(1)	−8(2)
C17	23(2)	25(2)	17(2)	5(2)	2(1)	−2(1)
C18	27(2)	25(2)	18(2)	3(2)	2(1)	6(1)
C19	34(2)	30(2)	29(2)	−2(2)	6(2)	2(2)
O1	34(1)	26(1)	20(1)	−3(1)	5(1)	−6(1)
O2	51(2)	19(1)	20(1)	−3(1)	3(1)	−8(1)
F1	23(1)	43(1)	45(1)	−22(1)	−4(1)	10(1)
F2	30(1)	56(2)	30(1)	14(1)	7(1)	−8(1)
F3	22(1)	41(1)	46(1)	−11(1)	6(1)	−11(1)
F4	32(1)	31(1)	40(1)	−2(1)	−10(1)	8(1)
F5	30(1)	20(1)	40(1)	−5(1)	2(1)	−5(1)
F6	26(1)	48(2)	25(1)	−2(1)	−6(1)	−6(1)
S1	22(1)	21(1)	22(1)	−3(1)	−1(1)	3(1)
S2	26(1)	21(1)	23(1)	−4(1)	2(1)	−2(1)